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5-SUBSTITUTED 2-(PHENYLMETHYL)THIO-4-PHENYL-4H-1,2,4-TRIAZOLE DERIVATIVES AND RELATED COMPOUNDS AS GABA-AGONISTS FOR THE TREATMENT OF URINARY INCONTINENCE AND RELATED DISEASES

DETAILED DESCRIPTION OF INVENTION

TECHNICAL FIELD

The present invention relates to a phenyltriazole derivative which is useful as an active ingredient of pharmaceutical preparations. The phenyltriazole derivative of the present invention has γ-aminobutyric acid receptor ($GABA_B$ receptor) agonistic activity, and can be used for the prophylaxis and treatment of diseases associated with $GABA_B$ receptor activity, in particular for the treatment of overactive bladder, urinary incontinence such as urge urinary incontinence, benign prostatic hyperplasia,spasticity and motor control, pain, epilepsy, cognitive defects, psychiatric disorders, alcohol dependence and withdrawal, feeding behaviour, cardiovascular, respiratory disorders and gastrointestinal disorders.

BACKGROUND ART

$GABA_B$ receptors are the first example of G protein-coupled receptors where heteromerization of two receptor subtypes has been demonstrated to be necessary for normal function (Jones et a/., Nature, (1998) 396, 674- 679); Kaupmann et al., Nature, (1998) 396, 683-687; Kuner et a/., Science, (1999) 283, 74-77). Currently there are two $GABA_B$ receptor subtypes known, $GABA_BR1$ and R2. In the brain there are two predominant N terminal splice variants expressed from the $GABA_B$ R1 gene, $GABA_BR1a$ and R1b, which heterodimerize with the R2 subunit. Pharmacologically, the different splice forms of $GABA_BR1$ could not be distinguished (Kaupmann et al., Nature, (1997) 386,239-246.

$GABA_B$ receptors are located throughout the central and peripheral nervous systems (see Ong and Kerr, Life Sciences, (1990) 46,1489-1501; Bowery et al., Drug Res. (1992) 42(1), 2a, 215-223), and are thus involved in the regulation of a wide variety of neurally-controlled physiological responses, from memory and learning to muscle contraction. This makes the $GABA_B$ receptor a target for pharmaceutical agents intended to treat central and peripheral neural disorders, and indeed a variety of $GABA_B$ agonists and antagonists are known and have been proposed for use in therapy including pain, spasticity and motor control, epilepsy, cognitive defects, psychiatric disorders, alcohol dependence and withdrawal, feeding behaviour, cardiovascular, respiratory disorders and gastrointestinal disorders (Bittiger et al., in GABA: Receptors, Transporters and Metabolism, Tanaka, C., and Bowery, N.G. (Eds). Birkhauser Verlag Basel/Switzerland (1996), 297-305; Bittiger et al., Trends Pharmacol. Sci., 14, 391-394,1993; Froestl et al., J. Med. Chem., 38, 3297-3312,1995; Froestl et al., Ibid., 3313-3331).

The $GABA_B$ receptor agonist baclofen given intrathecally is used clinically for reducing urethral resistance and detrusor overactivity associated with spasticity (Steers et al., *J. Urol.*, 148, 1849-1855,1992; Mertens et al., *Acta Neurochir.*, 64, 17-25 1995). The main effect of baclofen within the central nervous system is to reduce transmitter release. In the spinal cord it affects the activity of motoneurons and interneurons that are important for micturition and baclofen has previously been reported to have an inhibitory action on rat micturition after intrathecal administration (Igawa et al. *J. Urol.*, 150, 537-542, 1993; Pehrson et al. *J. Urol.*, 168, 2700-2705 ,2002).

Taken together, it is suggested that $GABA_B$ system is involved in the micturition control, both in animals and human. A potent and selective $GABA_B$ agonist can provide therapeutic benefit in the treatment of urinary bladder dysfunction as well as other indications described above.

$GABA_B$ agonists are also known to have smooth muscle relaxation action, thus a potent and selective $GABA_B$ agonist can provide therapeutic benefit in the treatment of BPH.

Urinary incontinence

UI is the involuntary loss of urine. UUI is one of the most common types of UI together with stress urinary incontinence (SUI) which is usually caused by a defect in the urethral closure mechanism. UUI is often associated with neurological disorders or diseases causing neuronal damages such as dementia, Parkinson's disease, multiple sclerosis, stroke and diabetes, although it also occurs in individuals with no such disorders. One of the usual causes of UUI is overactive bladder (OAB) which is a medical condition referring to the symptoms of frequency and urgency derived from abnormal contractions and instability of the detrusor muscle.

There are several medications for urinary incontinence on the market today mainly to help treating UUI. Therapy for OAB is focused on drugs that affect peripheral neural control mechanisms or those that act directly on bladder detrusor smooth muscle contraction, with a major emphasis on development of anticholinergic agents. These agents can inhibit the parasympathetic nerves which control bladder voiding or can exert a direct spasmolytic effect on the detrusor muscle of the bladder. This results in a decrease in intravesicular pressure, an increase in capacity and a reduction in the frequency of bladder contraction. Orally active anticholinergic drugs are the most commonly prescribed drugs. However, their most serious drawbacks are unacceptable side effects such as dry mouth, abnormal visions, constipation, and central nervous system disturbances. These side effects lead to poor compliance. Dry mouth symptoms alone are responsible for a 70% non-compliance rate with oxybutynin. The inadequacies of present therapies highlight the need for novel, efficacious, safe, orally available drugs that have fewer side effects.

Benign prostatic hyperplasia (BPH)

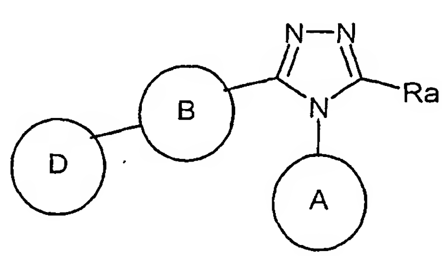
BPH is the benign nodular hyperplasia of the periurethral prostate gland commonly seen in men over the age of 50. The overgrowth occurs in the central area of the prostate called the transition zone, which wraps around the urethra. BPH causes variable degrees of bladder outlet obstruction resulting in progressive lower urinary tract syndromes (LUTS) characterized by urinary frequency, urgency, and nocturia due to incomplete emptying and rapid refilling of the bladder. The actual cause of BPH is unknown but may involve age-related alterations in balance of steroidal sex hormones.

The selective α1-adrenoceptor antagonists, such as prazosin, indoramin and tamsulosin are used as an adjunct in the symptomatic treatment of urinary obstruction caused by BPH, although they do not affect on the underlying cause of BPH. In BPH, increased sympathetic tone exacerbates the degree of obstruction of the urethra through contraction of prostatic and urethral smooth muscle. These compounds inhibit sympathetic activity, thereby relaxing the smooth muscle of the urinary tract. Uroselective α1-antagonists and α1-antagonists with high tissue selectivity for lower urinary tract smooth muscle that do not provoke hypotensive side-effects should be developed for the treatment.

Drugs blocking dihydrotestosterone have been used to reduce the size of the prostate. 5α-reductase inhibitors such as finasteride are prescribed for BPH. These agents selectively inhibit 5α-reductase which mediates conversion of testosterone to dihydrotestosterone, thereby reducing plasma dihydrotestosterone levels and thus prostate growth. The 5α-reductase inhibitors do not bind to androgen receptors and do not affect testosterone levels nor do they possess feminizing side-effects.

Androgen receptor antagonists are used for the treatment of prostatic hyperplasia due to excessive action or production of testosterone. Various antiandrogens are under investigation for BPH including chlormadione derivatives with no estrogenic activity, orally-active aromatase inhibitors, luteinizing hormone-releasing hormone (LHRH) analogues.

WO01/87855 discloses phenyltriazole derivatives represented by the general formula:



wherein

A represents optionally substituted aryl, etc;

B and D independently represent optionally substituted aryl, carbocycles, or 5-or 6-membered heterocycles;

Ra represents H, halgen-substituted alkyl, (un)substituted aryl, (un)substituted heterocycles, (un)substituted cycloalkyl, or –[Alk1]m-X^P-[Alk2]n-Y^P-$R1^P$;

wherein

$R1^P$ represents H, optionally substituted aryl, etc;

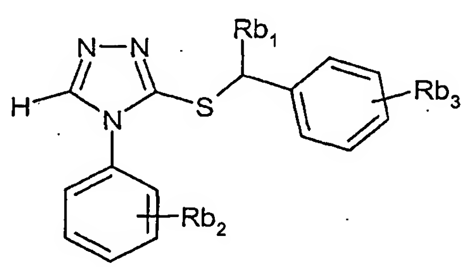
X^P represents direct bond, -O-, -S-, etc;

Y represents direct bond, m and n independently represent an integer of 0 or1;

Alk1 and Alk2 independently represent alkyl, etc,

as an inhibitor of glycine transporter.

Yamada, N. et al. discloses phenyltriazole derivatives represented by the general formula:



wherein

Rb_1 represents H, methyl, or ethyl;

Rb_2 represents H, chloro, fluoro, dichloro, methyl, methoxy, or trifluoromethyl;

Rb_3 represents H, chloro, methyl, ethyl, methoxy, ethoxy, fluoro, trifluoromethoxy, or dichloro,

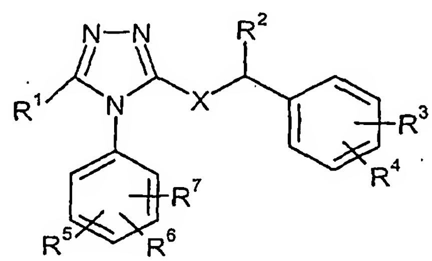
as a bleaching herbicide (Bioscience, Biotechnology, and Biochemistry (2002), 66(8), 1671-1676).

However, none of these references discloses phenyltriazole derivatives having $GABA_B$ receptor agonistic activity.

The development of a compound which has effective $GABA_B$ agonistic activity and can be used for the prophylaxis and treatment of diseases associated with $GABA_B$ receptor activity, in particular for the treatment of urinary incontinence, urge urinary incontinence, overactive bladder as well as pain, such as chronic pain, neuropathic pain, postoperative pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia or nerve injury induced pain, spasticity and motor control, epilepsy, cognitive defects, psychiatric disorders, alcohol dependence and withdrawal, feeding behaviour, cardiovascular, respiratory disorders and gastrointestinal disorders has been desired.

SUMMARY OF THE INVENTION

This invention is to provide phenyltriazole derivatives of the formula (I), their tautomeric and stereoisomeric form, and salts thereof:



wherein

R^1 represents alkyl optionally substituted by one or two substituents selected from the group consisting of alkoxy, amino, alkylamino, di(alkyl)amino, alkanoyloxy, hydroxy, carboxy, alkoxycarbonyl, cycloalkylphenyloxy, halogen, morpholino, carbamoyl, alkylsulfonyl-amino, phenyloxy optionally substituted by cycloalkyl, and 3- 8 membered saturated ring optionally having one or two N atom which ring optionally substituted by hydroxy or alkanoyl,

or 3-8 membered saturated or unsaturated ring optionally having one or two hetero atoms selected from the group consisting of N and O, and which ring is optionally substituted by one or two substituents selected from the group consisting of alkyl, halogen, alkoxy, nitro, amino, cyano, alkylamino, di(alkyl)amino, 4-7 membered saturated cyclic amine optionally substituted by hydroxy, and mono-, di-, or tri- halogen substituted alkyl;

R^2 represents $-COR^{21}$, $-(CH_2)_n-R^{21}$ or tert-butyl,

wherein

R^{21} is alkoxy, hydroxy, mono-, di-, or tri- halogen substituted alkyl,

or 3-8 membered saturated or unsaturated ring optionally having one or two heteroatoms selected from the group consisting of N, O, and S and which ring is optionally substituted by one or two substituents independently selected from the group consisting of alkanoyl, halogen, benzyl, alkoxycarbonyl, haloalkyloxy-carbonyl, cyano, hydroxy, amino, alkylamino, di(alkyl)amino, cycloalkylamino, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by alkoxycarbonyl or mono-, di-, or tri-halogen, alkoxy optionally substituted by mono-, di-, or tri- halogen, and alkylthio optionally substituted by mono-, di-, or tri- halogen;

n is 0 or 1;

R^3 and R^4 independently represent hydrogen, halogen, cyano, hydroxy, amino, alkylamino, di(alkyl)amino, cycloalkylamino, carboxy, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by hydroxy, alkoxycarbonyl or mono-, di-, or tri-halogen, alkoxy optionally substituted by mono-, di-, or tri- halogen, or alkylthio optionally substituted by mono-, di-, or tri- halogen;

R^5 represents hydrogen, hydroxy, nitro, cyano, halogen, sulfamoyl, alkylsulfonyl, alkyl-aminosulfonyl, di(alkyl)aminosulfonyl, $-(CH_2)_m-CO-R^{50}$, $-(CH_2)_m-R^{51}$, $-NR^{52}R^{53}$, or $-OR^{54}$,

wherein

m is 0, 1, 2, or 3

R^{50} is hydroxy, hydrogen, alkoxy, morpholino, di(phenyl)methyloxy, di(halogen substituted phenyl)methyloxy, $-NR^{501}R^{502}$ (wherein said R^{501} and R^{502} independently represent hydrogen, alkoxyalkyl, alkyl, hydroxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl or

R^{501} and R^{502} together form with the adjuscent N atom, morpholino, piperazino optionally substituted by oxo, or 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl) or alkyl optionally substituted by halogen,

R^{51} is hydrogen, hydroxy, or $-NR^{511}R^{512}$ (wherein said R^{511} and R^{512} independently represent hydrogen, alkoxyalkyl, alkyl, hydroxyalkyl, alkoxycarbonylalkyl, or

carboxyalkyl, or R^{511} and R^{512} together form with the adjuscent N atom, 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl),

R^{52} and R^{53} independently represent hydrogen, alkyl, hydroxy, cycloalkylcarbonyl, hydroxyalkyl, alkylsulfonyl, hydroxyalkylcarbonyl, carboxyalkylcarbonyl, alkanoyloxyalkylcarbonyl, or alkoxycarbonylalkylcarbonyl, or R^{52} and R^{53} together form with adjuscent N atom, morpholino, cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl,

R^{54} represents alkyl optionally substituted by morpholino, amino, di(alkyl)amino, carboxy, alkoxycarbonyl, or mono-, di-, or tri- halogen, or piperazino substituted by carboxy;

R^6 and R^7 independently represents hydrogen, morpholino, hydroxypyrrolidinylcarbonyl, hydroxyalkylaminocarbonyl, cyano, hydroxy, hydroxyalkyl, hydroxyamino, carboxy, fluoro, chloro, bromo, nitro, amino, alkylamino, di(alkyl)amino, cycloalkylamino, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, diphenylmethyloxycarbonyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by alkoxyalkyl(alkyl)amino, di(alkyl)amino, alkoxycarbonyl, carboxy, or mono-, di-, or tri-halogen, alkoxy optionally substituted by morpholino, di(alkyl)amino, or mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen

or R^6 and R^7 together form phenyl fused to adjacent phenyl; and

X represents $CR^{10}R^{11}$, NR^{12}, S, O, SO_2, or SO

wherein R^{10}, R^{11}, and R^{12} independently represent hydrogen or methyl.

The phenyltriazole derivatives of formula (I), their tautomeric and stereoisomeric form, and salts thereof surprisingly show excellent $GABA_B$ agonistic activity. They are, therefore, suitable especially for the prophylaxis and treatment of diseases associated with $GABA_B$ receptor activity, in particular for the treatment of urinary incontinence, urge urinary incontinence and/or overactive bladder.

The compounds of the present invention are also effective for treating or preventing a disease selected from the group consisting of pain, such as chronic pain, neuropathic pain, postoperative

pain, rheumatoid arthritic pain, neuralgia, neuropathies, algesia, or nerve injury induced pain, spasticity and motor control, epilepsy, cognitive defects, psychiatric disorders, alcohol dependence and withdrawal, feeding behaviour, cardiovascular, respiratory disorders and gastrointestinal disorders since the diseases also relate to $GABA_B$ receptor activity.

In another embodiment, the phenyltriazole derivatives of formula (I) are those wherein;

wherein

R^1 represents alkyl optionally substituted by one or two substituents selected from the group consisting of alkoxy, amino, alkylamino, di(alkyl)amino, alkanoyloxy, hydroxy, carboxy, alkoxycarbonyl, cycloalkylphenyloxy, halogen, morpholino, carbamoyl, phenyloxy optionally substituted by cycloalkyl, and 3- 8 membered saturated ring optionally having one or two N atom which ring optionally substituted by hydroxy or alkanoyl,

or 3-8 membered saturated or unsaturated ring optionally having one or two hetero atoms selected from the group consisting of N and O, and which ring is optionally substituted by one or two substituents selected from the group consisting of alkyl, halogen, alkoxy, nitro, amino, cyano, alkylamino, di(alkyl)amino, 4-7 membered saturated cyclic amine optionally substituted by hydroxy, and mono-, di-, or tri- halogen substituted alkyl;

R^2 represents $-COR^{21}$ or $-(CH_2)_n-R^{21}$,

wherein

R^{21} is alkoxy, hydroxy, mono-, di-, or tri- halogen substituted alkyl,

or 3-8 membered saturated or unsaturated ring optionally having one or two heteroatoms selected from the group consisting of N, O, and S and which ring is optionally substituted by one or two substituents independently selected from the group consisting of alkanoyl, halogen, benzyl, alkoxycarbonyl, haloalkyloxy-carbonyl, cyano, hydroxy, amino, alkylamino, di(alkyl)amino, cycloalkylamino, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by alkoxycarbonyl or mono-, di-, or tri-halogen, alkoxy optionally substituted by mono-, di-, or tri- halogen, and alkylthio optionally substituted by mono-, di-, or tri- halogen;

n is 0 or 1;

R^3 and R^4 independently represent hydrogen, halogen, cyano, hydroxy, amino, alkylamino, di(alkyl)amino, cycloalkylamino, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by alkoxycarbonyl or mono-, di-, or tri-halogen, alkoxy optionally substituted by mono-, di-, or tri- halogen, or alkylthio optionally substituted by mono-, di-, or tri- halogen;

R^5 represents hydrogen, hydroxy, nitro, cyano, halogen, sulfamoyl, alkylsulfonyl, alkyl-aminosulfonyl, di(alkyl)aminosulfonyl, $-(CH_2)_m-CO-R^{50}$, $-(CH_2)_m-R^{51}$, $-NR^{52}R^{53}$, or $-OR^{54}$,

wherein

m is 0, 1, 2, or 3

R^{50} is hydroxy, hydrogen, alkoxy, morpholino, di(phenyl)methyloxy, di(halogen substituted phenyl)methyloxy, $-NR^{501}R^{502}$ (wherein said R^{501} and R^{502} independently represent hydrogen, alkoxyalkyl, alkyl, hydroxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl or

R^{501} and R^{502} together form with the adjuscent N atom, morpholino, or 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl) or alkyl optionally substituted by halogen,

R^{51} is hydrogen, hydroxy, or $-NR^{511}R^{512}$ (wherein said R^{511} and R^{512} independently represent hydrogen, alkoxyalkyl, alkyl, hydroxyalkyl, alkoxycarbonylalkyl, or carboxyalkyl, or R^{511} and R^{512} together form with the adjuscent N atom, 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl),

R^{52} and R^{53} independently represent hydrogen, alkyl, hydroxy, cycloalkylcarbonyl, or hydroxyalkyl, or R^{52} and R^{53} together form with adjuscent N atom, morpholino, cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl,

R^{54} represents alkyl optionally substituted by morpholino, amino, di(alkyl) amino, or mono-, di-, or tri- halogen;

R^6 and R^7 independently represents hydrogen, morpholino, hydroxypyrrolidinylcarbonyl, hydroxyalkylaminocarbonyl, cyano, hydroxy, hydroxyalkyl, hydroxyamino, carboxy, fluoro, chloro, bromo, nitro, amino, alkylamino, di(alkyl)amino, cycloalkylamino, alkoxycarbonyl, sulfamoyl, alkylaminosulfonyl, di(alkyl)aminosulfonyl, alkanoyl, alkanoylamino, carbamoyl, diphenylmethyloxycarbonyl, alkylcarbamoyl, di-(alkyl)carbamoyl, alkylsulfonyl, alkyl optionally substituted by alkoxyalkyl(alkyl)amino, di(alkyl)amino, alkoxycarbonyl, carboxy, or mono-, di-, or tri-halogen, alkoxy optionally substituted by morpholino, di(alkyl)amino, or mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen

or R^6 and R^7 together form phenyl fused to adjacent phenyl; and

X represents $CR^{10}R^{11}$, NR^{12}, S, O, SO_2, or SO

wherein R^{10}, R^{11}, and R^{12} independently represent hydrogen or methyl.

Yet another embodiment of formula (I) can be those wherein:

X represents CH_2, NH, S, O, SO_2, or SO;

R^1 represents C_3 to C_8 cycloalkyl,

C_1-C_6 alkyl optionally substituted by one or two substituents selected from the group consisting of C_1-C_6 alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkanoyloxy, hydroxy, C_3-C_8 cycloalkyl, carboxy, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkylphenyloxy, halogen, morpholino, and pyrrolidinyl,

pyridyl, pyrrolidinyl, piperidinyl optionally substituted by methyl, or

phenyl optionally substituted by one selected from the group consisting of halogen, C_1-C_6 alkoxy, nitro, amino, cyano, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, and mono-, di- or tri-halogen substituted C_1-C_6alkyl,

R^2 represents $-COR^{21}$ or $-(CH_2)_n$-R^{21}, wherein R^{21} represents mono-, di-, tri- halogen substituted C_1-C_6 alkyl, morpholino, C_1-C_6 alkoxy, hydroxy, C_3 to C_8 cycloalkyl, pyridyl, furanyl, thiophenyl, pyrrolidinyl, piperidinyl optionally substituted by one substituent selected from the group consisting of benzyl, C_1-C_6 alkoxycarbonyl, and halo C_1-C_6 alkyloxycarbonyl, or phenyl optionally substituted by one substituent selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, and mono-, di-, or tri- halogen substituted C_1-C_6alkyl;

n is 0 or 1;

R^3 and R^4 independently represent hydrogen, halogen, cyano, hydroxy, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, C_{1-6} alkoxycarbonyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by C_{1-6} alkoxycarbonyl or mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen;

R^5 represents hydrogen, nitro, cyano, hydroxy, halogen, sulfamoyl, C_1-C_6alkylsulfonyl, C_1-C_6alkylaminosulfonyl, di(C_1-C_6alkyl)aminosulfonyl, -$(CH_2)_m$-CO-R^{50}, -$(CH_2)_m$-R^{51}, -$NR^{52}R^{53}$, or -OR^{54},

wherein m is 0, 1, 2, or 3

R^{50} is hydroxy, hydrogen, C_1-C_6alkoxy, morpholino, diphenylmethyloxy, -$NR^{501}R^{502}$ (wherein said R^{501} and R^{502} independently represent hydrogen, C_1-C_6alkoxyalkyl, C_1-C_6alkyl, hydroxy C_1-C_6alkyl, C_1-C_6alkoxycarbonyl C_1-C_6alkyl, or carboxy C_1-C_6alkyl or R^{501} and R^{502} together form with the adjacent N atom morpholino, 4-6 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl) or C_1-C_6 alkyl optionally substituted by halogen,

R^{51} is hydrogen, hydroxy, or –$NR^{511}R^{512}$ (wherein said R^{511} and R^{512} independently represent hydrogen, C_1-C_6 alkoxyalkyl, C_1-C_6 alkyl, hydroxyalkyl, C_1-C_6 alkoxycarbonylalkyl, or carboxyalkyl or R^{511} and R^{512} together form with the adjacent N atom, 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl)

R^{52} and R^{53} independently represent hydrogen, C_1-C_6 alkyl, hydroxy, C_3-C_8cycloalkylcarbonyl, or hydroxy C_1-C_6 alkyl or R^{52} and R^{53} together form with adjacent N atom, morpholino, 4-7 membered saturated cyclic amino optionally substituted by one substituent selected from the group consisting of carboxy, hydroxyalkyl, hydroxy, and carbamoyl

R^{54} represents alkyl optionally substituted by morpholino, amino, or di(alkyl) amino, or mono-, di-, or tri- halogen; and

R^6 and R^7 independently represent hydrogen, morpholino, hydroxypyrrolidinylcarbonyl, hydroxyC_1-C_6alkylaminocarbonyl, cyano, hydroxy, hydroxyC_1-C_6alkyl, hydroxyamino, carboxy, fluoro, chloro, bromo, nitro, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, C_{1-6} alkoxycarbonyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, diphenylmethyloxycarbonyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by alkoxyalkyl(alkyl)amino, di(alkyl)amino, C_{1-6} alkoxycarbonyl, carboxy, or mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by morpholino, di(alkyl)amino, or mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri- halogen

or R^6 and R^7 together form phenyl fused to adjacent phenyl.

Yet another embodiment of formula (I) can be those wherein:

X represents CH_2, NH, S, or SO;

R^1 represents cyclopropyl, pyridyl,

phenyl optionally substituted by halogen, C_1-C_6alkoxy, nitro, amino, cyano, C_1-C_6alkylamino, di(C_1-C_6alkyl)amino, or halogen substituted C_1-C_6alkyl,

C_1-C_6 alkyl optionally substituted by one or two substituents selected from the group consisting of C_1-C_6alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkanoyloxy, hydroxy, C_3-C_8 cycloalkyl, carboxy, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkylphenyloxy, halogen, morpholino, and pyrrolidinyl,

pyrrolidinyl, or piperidinyl optionally substituted by methyl;

R^2 represents $-COR^{21}$ or $-(CH_2)_n$-R^{21}, wherein R^{21} represents mono-, di- or tri- halogen substituted alkyl, morpholino, C_1-C_6alkoxy, hydroxy, C_3 to C_8 cycloalkyl, pyridyl, furanyl, thiophenyl, pyrrolidinyl, piperidinyl optionally substituted by one selected from the group consisting from benzyl, C_1-C_6alkoxycarbonyl, and haloC_1-C_6alkyloxycarbonyl, or phenyl optionally substituted by one selected from the group consisting of C_1-C_6 alkyl, halogen, C_1-C_6 alkoxy, and mono-, di- or tri- halogen substituted C_1-C_6alkyl;

n is 0 or 1;

R^3 and R^4 independently represent hydrogen, halogen, methyl, or amino;

R^5 represents hydrogen, morpholino, hydroxypyrrolidinylcarbonyl, hydroxyalkylaminocarbonyl, cyano, hydroxy, hydroxyalkyl, hydroxyamino, carboxy, fluoro, chloro, bromo, nitro, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, C_{1-6} alkoxycarbonyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, diphenylmethyloxycarbonyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by alkoxy-alkyl(alkyl)amino, di(alkyl)amino, C_{1-6} alkoxycarbonyl, carboxy, or mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by morpholino, di(alkyl)amino, or substituted by mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri-halogen; and

R^6 and R^7 represent hydrogen,

or R^6 and R^7 together form phenyl fused to adjacent phenyl.

Yet another embodiment of formula (I) can be those wherein:

X represents CH_2, NH, or S;

R^1 represents cyclopropyl, pyridyl, phenyl optionally substituted by halogen, alkoxy, nitro, amino, cyano, alkylamino, di(alkyl)amino, or halogen substituted alkyl,

C_1-C_6 alkyl optionally substituted by one or two substituents selected from the group consisting of alkoxy, amino, C_1-C_6 alkylamino, di(C_1-C_6 alkyl)amino, C_1-C_6 alkanoyloxy, hydroxy, C_3-C_8 cycloalkyl, carboxy, C_1-C_6 alkoxycarbonyl, C_3-C_8 cycloalkylphenyloxy, halogen, morpholino, and pyrrolidinyl,

pyrrolidiny, or piperidinyl optionally substituted by methyl.

Further, another embodiment of formula (I) can be those wherein:

X represents CH_2, NH, or S;

R^2 represents $-COR^{21}$, $-(CH_2)_nR^{21}$, wherein R^{21} is phenyl optionally substituted by C_1-C_6 alkyl, halogen, halogen substituted alkyl or alkoxy and n is 0 or 1.

Additional embodiment of formula (I) can be those wherein:

X represents CH_2, NH, or S;

R^3 and R^4 independently represent hydrogen, halogen, methyl, amino; and

R^5 represents hydrogen, morpholino, hydroxypyrrolidinylcarbonyl, hydroxyalkylamino-carbonyl, cyano, hydroxy, hydroxyalkyl, hydroxyamino, carboxy, fluoro, chloro, bromo, nitro, amino, C_{1-6} alkylamino, di(C_{1-6} alkyl)amino, C_{3-8} cycloalkylamino, C_{1-6} alkoxy-carbonyl, sulfamoyl, C_{1-6} alkylaminosulfonyl, di(C_{1-6} alkyl)aminosulfonyl, C_{1-6} alkanoyl, C_{1-6} alkanoylamino, carbamoyl, diphenylmethyloxycarbonyl, C_{1-6} alkylcarbamoyl, di-(C_{1-6} alkyl)carbamoyl, C_{1-6} alkylsulfonyl, C_{1-6} alkyl optionally substituted by alkoxy-alkyl(alkyl)amino, di(alkyl)amino, C_{1-6} alkoxycarbonyl, carboxy, or mono-, di-, or tri-halogen, C_{1-6} alkoxy optionally substituted by morpholino, di(alkyl)amino, or substituted by mono-, di-, or tri- halogen, or C_{1-6} alkylthio optionally substituted by mono-, di-, or tri-halogen; and

R^6 and R^7 represents hydrogen.

More preferably, said phenyltriazole derivative of the formula (I) is selected from the group consisting of:

(4-{3-cyclopropyl-5-[(diphenylmethyl)thio]-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine;

(4-{3-[(diphenylmethyl)thio]-5-ethyl-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine;

(4-{3-[(diphenylmethyl)thio]-5-propyl-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine;

[4-(3-cyclopropyl-5-{[(2-methylphenyl)(phenyl)methyl]thio}-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

[4-(3-{[bis(4-chlorophenyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

[4-(3-cyclopropyl-5-{[(4-methylphenyl)(phenyl)methyl]thio}-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

[4-(3-{[bis(4-fluorophenyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

[4-(3-{[(4-chlorophenyl)(phenyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

(4-{3-cyclobutyl-5-[(diphenylmethyl)thio]-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine;

(4-{3-butyl-5-[(diphenylmethyl)thio]-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine;

[4-(3-{[bis(4-methylphenyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

{4-[3-cyclopropyl-5-({phenyl[4-(trifluoromethyl)phenyl]methyl}thio)-4H-1,2,4-triazol-4-yl]phenyl}dimethylamine;

[4-(3-{[(4-chlorophenyl)(cyclohexyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

3-[(diphenylmethyl)thio]-5-ethyl-4-(4-isopropylphenyl)-4H-1,2,4-triazole;

{4-[3-{[bis(4-chlorophenyl)methyl]thio}-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]phenyl}dimethylamine;

[4-(3-{[bis(4-chlorophenyl)methyl]thio}-5-propyl-4H-1,2,4-triazol-4-yl)phenyl]dimethylamine;

3-(3-{[bis(4-chlorophenyl)methyl]thio}-5-propyl-4H-1,2,4-triazol-4-yl)benzoic acid;

3-{5-{[bis(4-chlorophenyl)methyl]thio}-4-[4-(dimethylamino)phenyl]-4H-1,2,4-triazol-3-yl}propan-1-ol;

3-[3-{[bis(4-chlorophenyl)methyl]thio}-5-(3-fluorophenyl)- 4H-1,2,4-triazol-4-yl]benzoic acid;

3-[3-{[bis(4-chlorophenyl)methyl]thio}-5-(3-fluorophenyl)- 4H-1,2,4-triazol-4-yl]phenol;

3-(3-{[bis(4-chlorophenyl)methyl]thio}-5-propyl-4H-1,2,3-triazol-4-yl)benzoic acid;

3-(3-{[bis(4-chlorophenyl)methyl]thio}-5-cyclopropyl-4H-1,2,4-triazol-4-yl)benzoic acid;

5-[3-{[bis(4-chlorophenyl)methyl]thio}-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]-2-(dimethylamino)benzoic acid;

1-[4-(3-{[bis(4-chlorophenyl)methyl]thio}-5-propyl-4H-1,2,4-triazol-4-yl)phenyl]-piperidine-3-carboxylic acid; and

1-{4-[3-{[bis(4-chlorophenyl)methyl]thio}-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]-phenyl}-piperidine-3-carboxylic acid

or the salt thereof.

Further, the present invention provides a medicament, which includes one of the compounds, described above and optionally pharmaceutically acceptable excipients.

Alkyl per se and "alk" and "alkyl" in alkenyl, alkynyl, alkoxy, alkanoyl, alkylamino, alkylamino-carbonyl, alkylaminosulphonyl, alkylsulphonylamino, alkoxycarbonyl and alkoxycarbonylamino represent a linear, branched alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl and n-hexyl.

"Alk" in alkanoylamino represent a linear, branched and cyclo alkyl radical having generally 1 to 6, preferably 1 to 4 and particularly preferably 1 to 3 carbon atoms, representing illustratively and preferably methyl, ethyl, n-propyl, isopropyl, tert-butyl, n-pentyl, n-hexyl, and cyclopropyl.

Alkoxy illustratively and preferably represents methoxy, ethoxy, n-propoxy, isopropoxy, tert-butoxy, n-pentoxy and n-hexoxy.

Alkylamino illustratively and preferably represents an alkylamino radical having one or two (independently selected) alkyl substituents, illustratively and preferably representing methylamino, ethylamino, n-propylamino, isopropylamino, tert-butylamino, n-pentylamino, n-hexyl-amino, N,N-dimethylamino, N,N-diethylamino, N-ethyl-N-methylamino, N-methyl-N-n-propylamino, N-isopropyl-N-n-propylamino, N-t-butyl-N-methylamino, N-ethyl-N-n-pentylamino and N-n-hexyl-N-methylamino.

4-7 membered saturated Cyclic amine illustratively and preferably represent pyrrolidine, piperidine, azepane, and azetidine.

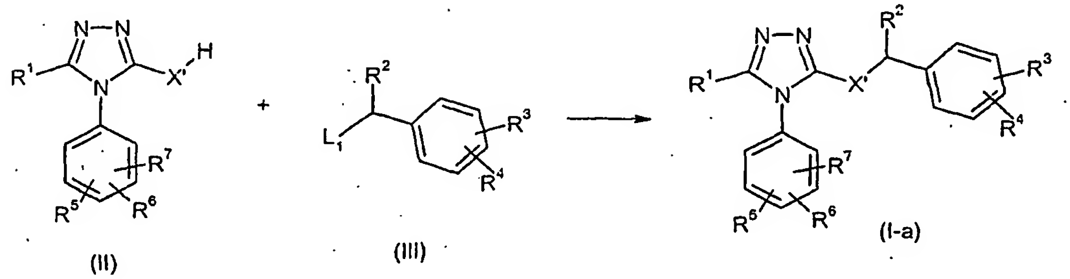
Heterocycle and/or heterocyclic as used herein, designate a closed ring structure, in which one or more of the atoms in the ring is a heteroatom such as sulfur, nitrogen, oxygen, and the like. Suitable examples include, without limitation, pyrrolidinyl, piperidino, piperazinyl, homo-piperidino, morpholinyl, thiomorpholinyl, tetrahydrofuryl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, pyridyl, pyrazinyl, pyrimidyl, pyridazinyl and the like.

EMBODIMENT OF THE INVENTION

The compound of the formula (I) of the present invention can be, but not limited to be, prepared by combining various known methods. In some embodiments, one or more of the substituents, such as amino group, carboxyl group, and hydroxyl group of the compounds used as starting materials or intermediates are advantageously protected by a protecting group known to those skilled in the art. Examples of the protecting groups are described in "Protective Groups in Organic Synthesis (3rd Edition)" by Greene and Wuts, John Wiley and Sons, New York 1999.

The compound of the formula (I-a) of the present invention can be, but not limited to be, prepared by the Method [A] below.

[Method A]



The compound of the formula (I-a) (wherein R^1, R^2, R^3, R^4, R^5, R^6 and R^7 are the same as defined above and X' represents O, S or NR^{12}) can be prepared by reacting the compound of the formula (II) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) with the compound of the formula (III) (wherein R^2, R^3 and R^4 are the same as defined above and L_1 represents a leaving group including, for instance, halogen atom such as chlorine, bromine, or iodine atom; C_{6-10} arylsulfonyloxy group such as benzenesulfonyloxy, or p-toluenesulfonyloxy; and C_{1-4} alkylsulfonyloxy group such as methanesulfonyloxy, and the like.)

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, iso-propyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethyl-formamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50 °C. The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

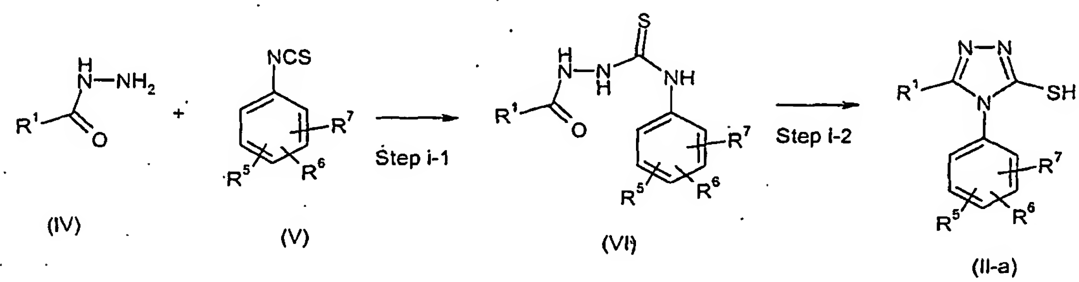
The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, or 4-dimethylaminopyridine, and inorganic base such as sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, or potassium bicarbonate, and others.

R^5, R^6, and/or R^7 of compound of the formula (I) can be further modified using conventional methods.

X' is further modified to be converted to SO or SO_2.

Preparation of intermediate (II-a)

[Method (i)]



The compound of the formula (II-a) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by the following procedures in two steps.

In Step i-1, the compound of the formula (VI) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (IV) (wherein R^1 is the same as defined above) with the compound of the formula (V) (wherein R^5, R^6 and R^7 are the same as defined above).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about room temperature to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 to 24 hours.

In Step i-2, the compound of the formula (II-a) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by cyclization reaction of the compound of the formula (VI) (wherein R^1, R^5, R^6 and R^7 are the same as defined above).

The reaction can be advantageously carried out in the presence of a base including, for instance, organic amines such as pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, or 4-dimethylaminopyridine, and inorganic base such as sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, or potassium bicarbonate, and others.

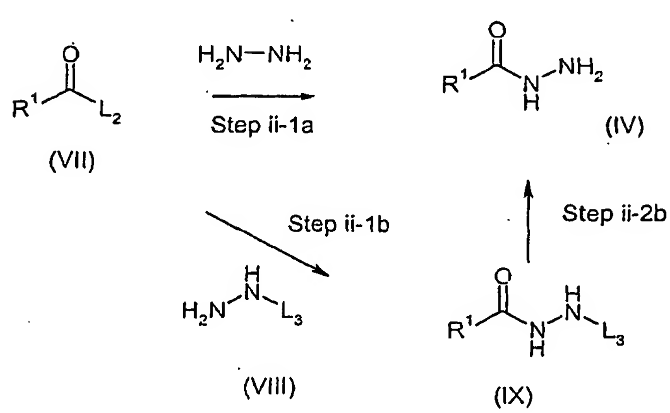
The reaction can be carried out in a solvent including, for instance, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

The compound of the formula (V) is commercially available or can be prepared by the use of known techniques.

Preparation of intermediate (IV)

[Method (ii)]



In step ii-1a, the compound of the formula (IV) (wherein R^1 is the same as defined above) can be prepared by reacting the compound of the formula (VII) (wherein R^1 is the same as defined above and L_2 represents a leaving group including, for instance, halogen atom such as chlorine, bromine, or iodine atom, hydroxy and C_{1-6} alkoxy) with hydrazine (free base, its salt or its hydrate).

The reaction can be carried out in a solvent including, for instance, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 0°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

Alternatively, the compound of the formula (IV) can be prepared by the following procedures.

In Step ii-1b, the compound of the formula (IX) (wherein wherein R^1 is the same as defined above and L_3 represents a protecting group including, for instance, tert-butoxycarbonyl) can be prepared by reacting the compound of the formula (VII) (wherein R^1 and L_2 are the same as defined above) with the compound of the formula (VIII) (wherein L_3 is the same as defined above).

When L_2 is hydroxy, the reaction can be done using a coupling agent including, for instance, carbodiimides such as N, N-dicyclohexylcarbodiimide and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide, benzophenyltriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), diphenylphosphoryl azide. N-hydroxysuccinimide, 1-hydroxybenzotiazole monohydrate (HOBt), and the like can be used as an accelerator of the reaction.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

In Step ii-2b, the compound of the formula (IV) (wherein R^1 is the same as defined above) can be prepared by removing the protecting group L_3 of the compound of the formula (IX) (wherein R^1 and L_3 are the same as defined above).

The removal of protective group L_3 can be done by using a reagent including, for instance, an acid such as trifluoroacetic acid and hydrochloric acid.

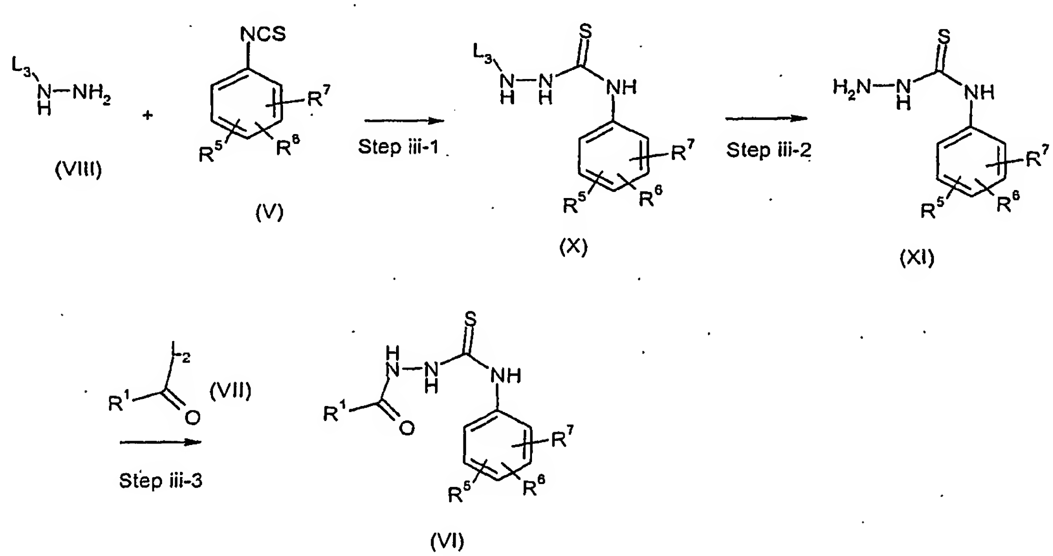
The reaction may be carried out without solvent or in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on compoundss to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 120°C. The reaction may be conducted for, usually, 30 minutes to 60 hours and preferably 1 to 48 hours.

Hydrazine (free base, its salt or its hydrate), the compound of the formula (VII) and (VIII) are commercially available or can be prepared by the use of known techniques.

Alternative procedures for the preparation of intermediate (VI)

[Method (iii)]



The compound of the formula (VI) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be alternatively prepared by the following procedures in three steps.

In Step iii-1, the compound of the formula (X) (wherein wherein L_3, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (VIII) (wherein L_3 is the

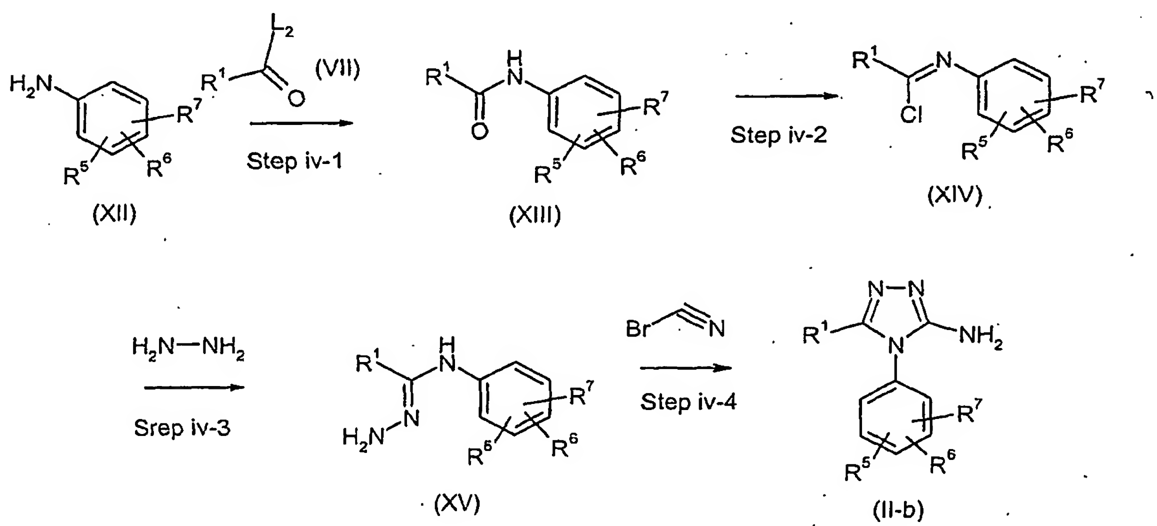
same as defined above) with the compound of the formula (V) (wherein R^5, R^6 and R^7 are the same as defined above) in a similar manner described in Step i-1 for the preparation of compounds of the formula (VI).

In Step iii-2, the compound of the formula (XI) (wherein R^5, R^6 and R^7 are the same as defined above) can be prepared by removing the protecting group L_3 of the compound of the formula (X) (wherein L_3, R^5, R^6 and R^7 are are the same as defined above) in a similar manner described in Step ii-2b for the preparation of compounds of the formula (IV).

In Step iii-3, the compound of the formula (VI) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (XI) (wherein R^5, R^6 and R^7 are the same as defined above) with the compound of the formula (VII) (wherein R^1 and L_2 are the same as defined above) in a similar manner described in Step ii-1a for the preparation of compounds of the formula (IV).

Preparation of intermediate (II-b)

[Method (iv)]



The compound of the formula (II-b) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by the following procedures.

In Step iv-1, the compound of the formula (XIII) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (XII) (wherein R^5, R^6 and R^7 are the same as defined above) with the compound of the formula (VII) (wherein R^1 and L_2 are the same as defined above).

When L_2 is hydroxy, the reaction can be done using a coupling agent including, for instance, carbodiimides such as N, N-dicyclohexylcarbodiimide and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide, benzophenyltriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBOP), diphenylphosphoryl azide. N-hydroxysuccinimide, 1-hydroxybenzotiazole monohydrate (HOBt), and the like can be used as an accelerator of the reaction.

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, iso-propyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethyl-formamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

In Step iv-2, the compound of the formula (XIV) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (XIII) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) with an appropriate halogenating reagent including, for instance, $SOCl_2$, $POCl_3$, and the like.

The reaction may be carried out without solvent or in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

In Step iv-3, the compound of the formula (XV) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (XIV) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) with hydrazine (free base, its salt or its hydrate).

The reaction may be carried out in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; nitriles such as acetonitrile; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide (DMAC) and N-methylpyrrolidone (NMP); urea such as 1,3-dimethyl-2-imidazolidinone (DMI); sulfoxides such as dimethylsulfoxide (DMSO); and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about 0°C to 180°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 12 hours.

In Step iv-4, the compound of the formula (II-b) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) can be prepared by reacting the compound of the formula (XV) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) with cyanogen halides such as cyanogen bromide.

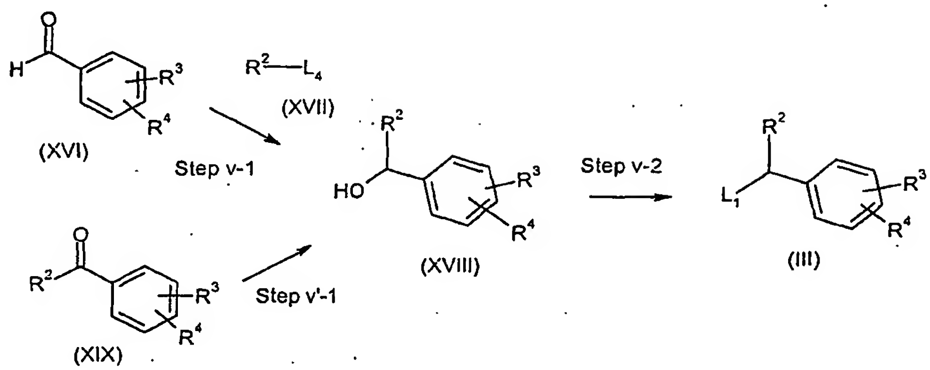
The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene; amides such as N, N-dimethylformamide (DMF), N, N-dimethylacetamide and N-methylpyrrolidone; alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature is usually, but not limited to, about -10°C to 200°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 1 hour to 24 hours.

The compound of the formula (XII) is commercially available or can be prepared by the use of known techniques.

Preparation of intermediate (III)

[Method (v)]



The compound of the formula (III) (wherein R^2, R^3 and R^4 are the same as defined above) can be prepared by the following procedures.

In Step v-1, the compound of the formula (XVIII) (wherein wherein R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (XVI) (wherein R^3 and R^4 are the same as defined above) with the compound of the formula (XVII) (wherein R^2 is the same as defined above and L_4 represents metal or metal complex including, for instance, lithium, magnesium chloride and magnesium bromide).

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aliphatic hydrocarbons such as n-hexane, cyclohexane; aromatic hydrocarbons such as benzene, toluene and xylene; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about -20°C to 50°C.

The reaction may be conducted for, usually, 30 minutes to 10 hours and preferably 1 to 24 hours.

The compound of the formula (XVIII) (wherein wherein R^2, R^3 and R^4 are the same as defined above) can be alternatively prepared by reacting the compound of the formula (XIX) (wherein R^2, R^3 and R^4 are the same as defined above) with a reducing agent including, for instance, sodium borohydride or lithium aluminum hydride as shown in Step v'-1.

The reaction may be carried out in a solvent including, for instance, ethers such as diethyl ether, isopropyl ether, dioxane and tetrahydrofuran (THF) and 1,2-dimethoxyethane; aliphatic hydro-

carbons such as n-hexane, cyclohexane; aromatic hydrocarbons such as benzene, toluene and xylene; and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50°C.

The reaction may be conducted for, usually, 30 minutes to 24 hours and preferably 1 to 10 hours.

In Step v-2, the compound of the formula (III) (wherein L_1, R^2, R^3 and R^4 are the same as defined above) can be prepared by reacting the compound of the formula (XVIII) (wherein wherein R^2, R^3 and R^4 are the same as defined above) with an appropriate halogenating reagent including, for instance, $POCl_3$, PCl_3, $SOCl_2$, and the like; or with the corresponding sulfonyl chloride for instance methanesulfonyl chloride.

The reaction may be carried out without solvent or in a solvent including, for instance, halogenated hydrocarbons such as dichloromethane, chloroform and 1,2-dichloroethane; ethers such as dioxane and tetrahydrofuran (THF)and 1,2-dimethoxyethane; aromatic hydrocarbons such as benzene, toluene and xylene, and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

The reaction can be advantageously conducted in the presence of a base, including, for instance, pyridine, triethylamine and N,N-diisopropylethylamine, dimethylaniline, diethylaniline, and others.

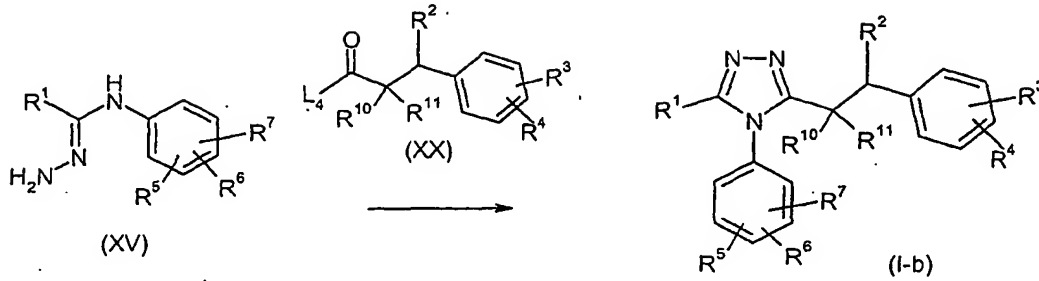
The reaction temperature is usually, but not limited to, about 0°C to 200°C and preferably about 20°C to 100°C. The reaction may be conducted for, usually, 30 minutes to 48 hours and preferably 2 hours to 24 hours.

The compound of the formula (XVI), (XVII) and (XIX) are commercially available or can be prepared by the use of known techniques.

Preparation of compound of (I-b)

The compound of the formula (I-b) of the present invention can be, but not limited to be, prepared by the Method [B] below.

[Method B]



The compound of the formula (I-b) (wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^{10} and R^{11} are the same as defined above) can be prepared by reacting the compound of the formula (XV) (wherein R^1, R^5, R^6 and R^7 are the same as defined above) with the compound of the formula (XX) (wherein R^2, R^3, R^4, R^{10} and R^{11} are the same as defined above and L_4 represents a leaving group including, for instance, halogen atom such as chlorine, bromine, or iodine atom).

The reaction can be carried out in a solvent including, for instance, alcohols such as methanol, ethanol, 1-propanol, isopropanol and tert-butanol, water and others. Optionally, two or more of the solvents selected from the listed above can be mixed and used.

he reaction temperature can be optionally set depending on the compounds to be reacted. The reaction temperature is usually, but not limited to, about 20°C to 50 °C. The reaction may be conducted for, usually, 30 minutes to 24 hours and preferably 1 to 10 hours.

The compound of the formula (XX) is commercially available or can be prepared by the use of known techniques..

When the compound shown by the formula (I) or a salt thereof has an asymmetric carbon in the structure, their optically active compounds and racemic mixtures are also included in the scope of the present invention.

Typical salts of the compound shown by the formula (I) include salts prepared by reaction of the compounds of the present invention with a mineral or organic acid, or an organic or inorganic base. Such salts are known as acid addition and base addition salts, respectively.

Acids to form acid addition salts include inorganic acids such as, without limitation, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, hydriodic acid and the like, and organic acids, such as, without limitation, p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like.

Base addition salts include those derived from inorganic bases, such as, without limitation, ammonium hydroxide, alkaline metal hydroxide, alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases, such as, without limitation, ethanolamine, triethylamine, tris(hydroxymethyl)aminomethane, and the like. Examples of inorganic bases include sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

The compound of the present invention or a salt thereof, depending on its substituents, may be modified to form lower alkylesters or known other esters; and/or hydrates or other solvates. Those esters, hydrates, and solvates are included in the scope of the present invention.

The compound of the present invention may be administered in oral forms, such as, without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions. They may also be administered in parenteral forms, such as, without limitation, intravenous, intraperitoneal, subcutaneous, intramuscular, and the like forms, well-known to those of ordinary skill in the pharmaceutical arts. The compounds of the present invention can be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using transdermal delivery systems well-known to those of ordinary skilled in the art.

The dosage regimen with the use of the compounds of the present invention is selected by one of ordinary skill in the arts, in view of a variety of factors, including, without limitation, age, weight, sex, and medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed.

The compounds of the present invention are preferably formulated prior to administration together with one or more pharmaceutically-acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Yet another embodiment of the present invention is pharmaceutical formulation comprising a compound of the invention and one or more pharmaceutically-acceptable excipients that are compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Pharmaceutical formulations of the invention are prepared by combining a therapeutically effective amount of the compounds of the invention together with one or more pharmaceutically-acceptable excipients therefore. In making the compositions of the present invention, the active ingredient may be mixed with a diluent, or enclosed within a carrier, which may be in the form of a

capsule, sachet, paper, or other container. The carrier may serve as a diluent, which may be solid, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments, containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions and sterile packaged powders.

For oral administration, the active ingredient may be combined with an oral, and non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, sodium carbonate, mannitol, sorbitol, calcium carbonate, calcium phosphate, calcium sulfate, methyl cellulose, and the like; together with, optionally, disintegrating agents, such as, without limitation, maize, starch, methyl cellulose, agar bentonite, xanthan gum, alginic acid, and the like; and optionally, binding agents, for example, without limitation, gelatin, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid, sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like.

In powder forms, the carrier may be a finely divided solid which is in admixture with the finely divided active ingredient. The active ingredient may be mixed with a carrier having binding properties in suitable proportions and compacted in the shape and size desired to produce tablets. The powders and tablets preferably contain from about 1 to about 99 weight percent of the active ingredient which is the novel composition of the present invention. Suitable solid carriers are magnesium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid formulations include suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carriers, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The formulation may be in unit dosage form, which is a physically discrete unit containing a unit dose, suitable for administration in human or other mammals. A unit dosage form can be a capsule or tablets, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more excipients. The quantity of active ingredient in a unit dose may be

varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

Typical oral dosages of the present invention, when used for the indicated effects, will range from about 0.01 mg/kg/day to about 100 mg/kg/day, preferably from 0.1 mg/kg/day to 30 mg/kg/day, and most preferably from about 0.5 mg/kg/day to about 10 mg/kg/day. In the case of parenteral administration, it has generally proven advantageous to administer quantities of about 0.001 to 100mg /kg/day, preferably from 0.01 mg/kg/day to 1 mg/kg/day. The compounds of the present invention may be administered in a single daily dose, or the total daily dose may be administered in divided doses, two, three, or more times per day. Where delivery is via transdermal forms, of course, administration is continuous.

EXAMPLES

The present invention will be described as a form of examples, but they should by no means be construed as defining the metes and bounds of the present invention.

In the examples below, all quantitative data, if not stated otherwise, relate to percentages by weight.

Mass spectra were obtained using electrospray (ES) ionization techniques (micromass Platform LC). Melting points are uncorrected. TLC was performed on a precoated silica gel plate (Merck silica gel 60 F-254). Silica gel (WAKO-gel C-200 (75-150 μm)) was used for all column chromatography separations. All chemicals were reagent grade and were purchased from Sigma-Aldrich, Wako pure chemical industries, Ltd., Great Britain, Tokyo kasei kogyo Co., Ltd., Nacalai tesque, Inc., Watanabe Chemical Ind. Ltd., Maybridge plc, Lancaster Synthesis Ltd., Merck KgaA, Germany, Kanto Chemical Co., Ltd.

Analytical HPLC Retention *times of intermediates and examples are measured as follows:*

Method A

Equipment: Waters 2690 separation module

Column temperature: 40 °C.

Mobile phase: water / acetonitrile (each of them containing 10mM ammonium acetate)

Column: Chromolith Rash RP-18e, 25 * 4.6mm

Flow rate: 1.3 mL/min.

Injection volume: 5 μL

Gradient (Time) : (water / acetonitrile)

0 Minutes : 9 / 1

0.2 Minutes: 9 / 1

2.0 Minutes: 1 / 9

3.5 Minutes: 1 / 9

4.0 Minutes: 9 / 1

Method B

Equipment: Hewlett Packard series 1100

Column temperature: 40 °C.

Mobile phase: water / acetonitrile (each of them containing 10mM ammonium acetate)

Column: YMC PackPro C-18, 35 * 4.6mm

Flow rate: 1.0 mL/min.

Injection volume: 5 microL

Gradient (Time) : (water / acetonitrile)

1 Minutes : 9 / 1

0.1 Minutes: 9 / 1

1.5 Minutes: 1 / 9

3.5 Minutes: 1 / 9

4.5 Minutes: 9 / 1

Method C

Equipment: Hewlett Packard series 1100

Column temperature: 40 °C.

Mobile phase: water / acetonitrile (each of them containing 10mM ammonium acetate)

Column: Phenomenex Luna 3u C18(2) 30 * 4.6mm

Flow rate: 1.0 mL/min.

Injection volume: 10 microL

Gradient (Time) : (water / acetonitrile)

2 Minutes : 9 / 1

0.5 Minutes: 9 / 1

4.5 Minutes: 1 / 9

6.5 Minutes: 1 / 9

8.5 Minutes: 9 / 1

HPLC-Methods:

Analytical HPLC as follows were determined on a HP 1100 with DAD-detection (Hewlett Packard) under the following conditions:

Method 2A

Column: Kromasil C18 60*2 at 30 °C; injection volume: 1.00 µl; flowrate: 0.75 ml/min; eluent: A= 0.01 M H_3PO_4 in H_2O, B= CH_3CN; gradient [t(min): A/B]: 0.0: 90/10; 0.5: 90/10; 4.5: 10/90; 8.0: 10/90; 8.5: 90/10 10.0: 90/10.

Method 2B

Column: Kromasil C18 60*2 at 30 °C; injection volume: 0.20 - 0.30 µl; flowrate: 0.75 ml/min; eluent: A= 0.01 M H_3PO_4 in H_2O, B= CH_3CN; gradient [t(min): A/B]: 0.0: 90/10; 0.5: 90/10; 4.5: 10/90; 6.5: 10/90; 7.5: 90/10.

Method 2C

Column: Kromasil C18 60*2 at 30 °C; injection volume: 1.0 µl; flowrate: 0.75 ml/min; eluent: A= 5ml 70% $HClO_4$/1L H_2O, B= CH_3CN; gradient [t(min): A/B]: 0.0: 98/2; 0.5: 98/2; 4.5: 10/90; 6.5: 10/90; 6.7: 98/2; 7.5: 98/2.

LC/MS-Methods:

Retention times for peaks with the correct product mass were recorded as follows:

Method 2D

Instrument MS: Micromass TOF (LCT); instrument HPLC: Waters2690; column: YMC-ODS-AQ, 50 mm x 2.0 mm, 3.0 µm; eluent A: water + 0.1% formic acid, eluent B: CH_3CN + 0.1% formic acid; gradient: 0.0 min 100%A → 0.2 min 100%A → 2.9 min 30%A → 3.1 min 10%A → 4.5 min 10%A → 4.51 min 100%A→ 6.5 min 100%A; oven: 40°C; flow rate: 0.8 ml/min; UV-detection: 210 nm.

Method 2E

Instrument MS: Micromass ZQ; instrument HPLC: Waters Alliance 2790; column: Uptisphere C 18, 50 mm x 2.0 mm, 3.0 µm; eluent A: water + 0.05% formic acid, eluent B: CH_3CN + 0.05% formic acid; gradient: 0.0 min 5%B → 2.0 min 40%B → 4.5 min 90%B→ 5.5 min 90%B; oven: 45°C; flow rate: 0.0 min 0.75 ml/min → 4.5 min 0.75 ml/min→ 5.5 min 1.25 ml/min; UV-detection: 210 nm.

^{1}H NMR spectra were recorded using either Bruker DRX-300 (300 MHz for ^{1}H) spectrometer or Brucker 500 UltraShieled™ (500 MHz for 1H) . Chemical shifts are reported in parts per million (ppm) with tetramethylsilane (TMS) as an internal standard at zero ppm. Coupling constant (J) are given in hertz and the abbreviations s, d, t, q, m, and br refer to singlet, doublet, triplet, quartet, multiplet, and broad, respectively. The mass determinations were carried out by MAT95 (Finnigan MAT).

All starting materials are commercially available or can be prepared using methods cited in the literature.

The effect of the present compounds was examined by the following assays and pharmacological tests.

[Measurement of change of intracellular cAMP accumulation by luciferase detection in the human $GABA_B$ receptor-transfected HEK293 cell line] (Assay 1)

(1) Cloning of $GABA_B$ receptors and generation of stable cell lines

The human $GABA_{B(1a)}$, $GABA_{B(1b)}$ and $GABA_{B(2)}$ receptor subunits were cloned into pcDNA3 (Invitrogen) as previously described (White J. H. et al., Nature 1998, 396(6712):679-82). The cell culture and transfection of Human Embryonic Kidney (HEK293) cells was done as follows. HEK293-Luc cells were grown in Dulbecco's modified Eagle's medium (DMEM, Gibco BRL) supplemented with 5% modified bovine serum (MBS, Gibco BRL) in fibronectin coated 96-well microtiter plates. For transfection (mammalian transfection kit; Stratagene) cells were grown at 20000 cells per well at 35 °C with 3% CO_2 for 24 h with 0.1 ml per well. DNA suspension: 10 µg expression plasmid DNA of each human $GABA_{B(1a)}$ and human $GABA_{B(2)}$ in pcDNA3 was dissolved in 450 µl of water with 50 ml $CaCl_2$ (2.5 M) + 500 µl 2x phosphate buffered saline (PBS, pH 6.95) and incubated for 10 to 20 min at room temperature. In the meantime cell medium was aspirated and cells were washed twice with 200 µl PBS per well and then 200 µl medium plus 5% MBS was added. For transfection 20 µl of

suspended DNA was added and incubated for 3 h at 35 °C with 3% CO_2, cells were washed with PBS and 200 μl of growth medium was added and cells were grown for 2 days. Cells were then trypsinized and diluted 1:10 in fibronectin coated wells and incubated with growth medium supplemented with 1 mg/ml G418 (Gibco BRL) and grown under selection pressure for 10 days with 2-3 medium changes. After G418 selection cells were grown until colonies had formed.

(2) Folskolin-stimulated luciferase-reporter gene assay

$GABA_{B(1b/2)}$-HEK293/CRE-luc cells were seeded into poly-D-lysine-coated 384-well white/opaque plates (BD BIOCOAT) at 4000 cells/well in 40 μl DMEM/F12 medium supplemented with 2.5% FBS, and grown for 48 hours at 37□ in a humidified atmosphere with 5% CO_2. Test compounds dissolved in DMSO were diluted into DMEM/F12 medium containing 0.1% BSA and transferred to the test cultures at 5 μl/well. 10 minutes after the test compound addition, forskolin prepared in a manner similar to the test compounds was added at 5 μl/well (1.6 μM of final concentration), and cells were then incubated for 3 hours at 37□ in 5% CO_2. After the incubation, the medium was discarded, followed by addition of 20 μl/well of 1:1 mixture of Steady-Glo™ reagent (Promega) and Phenol-red free DMEM/F12 medium. The plates were incubated at least 5 minutes to ensure complete cell lysis and then luciferase activity was measured with ViewLux microplate imager (Perkin Elmer).

[Measurement of rhythmic bladder contraction in anesthetized rats] (Assay 2)

(1) Animals

Female Sprague-Dawley rats (200~250 g / Charles River Japan) were used.

(2) Rhythmic bladder contraction in anesthetized rats

Rats were anesthetized by intraperitoneal administration of urethane (Sigma) at 1.25 g/kg. The trachea was cannulated with a polyethylene tube (HIBIKI, No.8) to facilitate respiration; and a cannula (BECTON DICKINSON, PE-50) was placed in the left femoral vein for intravenous administration of testing compounds. The abdomen was opened through a midline incision, and after both ureters were cut, a water-filled baloon (about 1 ml capacity) was inserted through the apex of the bladder dome. The baloon was connected to a pressure transducer onto a polygraph. Rhythmic bladder contraction was elicited by raising up intravesical pressure to approximately 15 cm H_2O. After the rhythmic bladder contraction was stable, a testing compound was administered

intravenously. Activity was estimated by measuring disappearance time and amplitude of the rhythmic bladder contraction. The effect on amplitute of bladder contractions was expressed as a percent suppression of the amplitude of those after the disappearance was recovered. Experimental values were expressed as the mean±S.E.M. The testing compounds–mediated inhibition of the rhythmic bladder contraction was evaluated using Student's t-test. A probability level less than 5% was accepted as significant difference.

Results in folskolin-stimulated luciferase-reporter gene assay (Assay 1) are shown in Examples and tables of the Examples below. For practical reasons, the compounds are grouped in four classes based on activity as follows:

IC_{50} = A (< or =) 0.1 μM < B (< or =) 0.5 μM < C (< or =) 1 μM < D

[Cystometry in anesthetized rats] (Assay 3)

Effect of a compound on cystometric parameters in rats were studied as described previously [Takeda H et al: J. Pharmacol. Exp. Ther. 126: 939- 945, 2000].

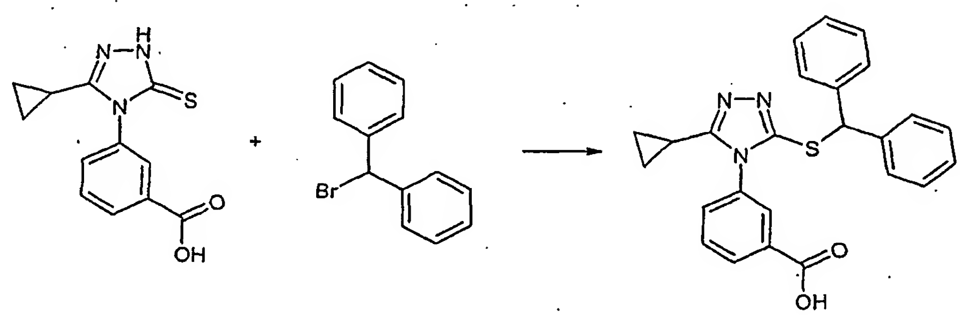
Female rats, weighing from 200 to 230 g, were anesthetized with urethane (1.2 g/kg i.p.). Through a midline abdominal incision, the ureter on each side was ligated and cut proximal to the ligature. A polyethylene catheter (PE-50) was inserted into the urinary bladder and connected through a three-way connector to: 1) a pressure transducer (Viggo-Spectramed Pte Ltd, DT-XXAD) for measurement of bladder pressure, and 2) a syringe infusion pump (TERUMO) for continuous infusion of saline into the bladder. During cystometry, saline was infused at a rate of 2.4 ml/h. Bladder pressure was recorded continuously on a PowerLab systems (BioResearch Center). The following cystometric parameters were obtained: micturition interval and micturition pressure (maximum bladder pressure during micturition). Two reproducible micturition cycles were recorded before drug administration and used to provide a baseline value to be compared with the first two micturition cycles just after drug administration. Relative values for the various cystometric parameters were calculated as follows: (mean value from two micturition cycles just after drug administration)/(mean value from two micturition cycles just before drug administration). A venous catheter was inserted into the left femoral vein for drug injection.

Z used in Melting point in the following section indicates decomposition.

[Example 1-1]

Method A

3-(3-benzhydrylsulfanyl-5-cyclopropyl-[1,2,4]triazol-4-yl)-benzoic acid



A solution of 3-(3-cyclopropyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)benzoic acid (152 mg, 0.58 mmol) in N,N-dimethylformamide (1 mL) was added potassium carbonate (403 mg, 2.91 mmol) and bromodiphenylmethane (187 mg, 0.76 mmol), and the mixture was stirred at 60 °C for 16 hours. The inorganic salts were filtered, and the filtrate was diluted with aqueous sodium bicarbonate solution. The mixture was washed with ethylacetate, and the aqueous layer was acidified to pH 2 with 1N aqueous HCl solution. The mixture was extracted with ethylacetate, and the organic layer was concentrated under reduced pressure. The obtained residue was recrystallized from the mixture of dichloromethane, diethylether, and hexane to provide 3-{3-cyclopropyl-5-[(diphenylmethyl)thio]-4H-1,2,4-triazol-4-yl}benzoic acid (65.9 mg).

^{1}H NMR (DMSO-d_6): δ 0.82-0.89 (m, 4H), 1.48-1.53 (m, 1H), 5.88 (s, 1H), 7.21-7.30 (m, 10H), 7.55 (d, J = 7.9 Hz, 1H), 7.70-7.74 (m, 2H), 8.12 (d, J = 7.9 Hz, 1H), 13.40 (s(br), 1H).

mp 193 °C;

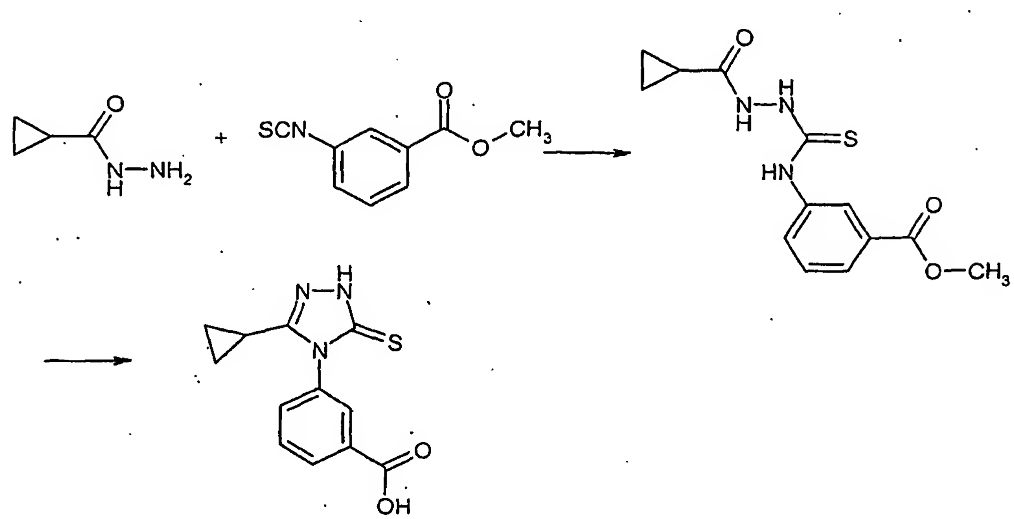
Molecular weight : 427.53

MS (M+H): 428

Activity Class : B

Preparation of intermediates

Method (i)



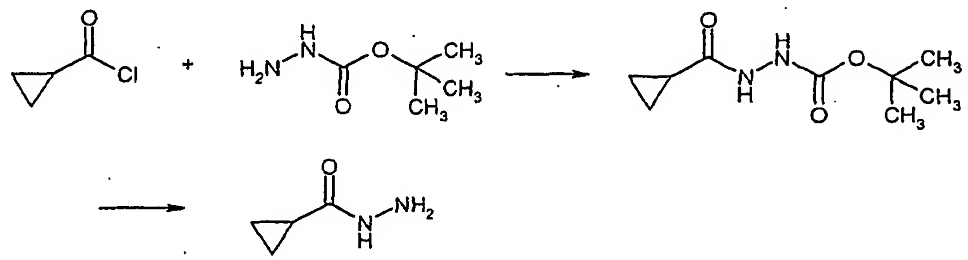
A mixture of cyclopropanecarbohydrazide (255 mg, 2.55 mmol) and methyl 3-isothiocyanato-benzoate (492 mg, 2.55 mmol) in ethanol (3 mL) was stirred at refluxing temperature for 16 hours. The mixture was concentrated under reduced pressure, and to the obtained residue was added a solution mixture of diethylether and hexane. The precipitates were collected and dried to afford methyl 3-({[2-(cyclopropylcarbonyl)hydrazino]carbonothioyl}amino) benzoate (399 mg). ^{1}H NMR (DMSO-d_6) δ 0.77-0.79 (m, 4H), 1.60-1064 (m, 1H), 3.32 (s, 3H), 7.47 (t, J = 7.9 Hz, 1H), 7.73 (d, J = 7.3 Hz, 1H), 7.80 (d, J = 7.3 Hz, 1H), 8.08 (s(br), 1H), 9.86 (s(br), 1H), 10.10 (s(br), 1H); ; MS m/z 294 (M^{+}+1).

Next, a solution of methyl 3-({[2-(cyclopropylcarbonyl)hydrazino]carbonothioyl}amino) benzoate (399 mg, 1.36 mmol) in 4N aqueous solution of sodium hydroxide (7 mL) was stirred at refluxing temperature for 16 hours. After having cooled to ambient temperature, the mixture was acidified to pH 2 with 1N aqueous solution of HCl. The mixture was extracted with ethylacetate, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 3-(3-cyclopropyl-5-thioxo-1,5-dihydro-4H-1,2,4-triazol-4-yl)benzoic acid (355 mg). ^{1}H NMR (DMSO-d_6) δ 0.77-0.92 (m, 4H), 1.47-1.52 (m, 1H), 7.70-7.77 (m, 2H), 8.01 (s, 1H), 8.09 (d, J = 6.3 Hz, 1H), 13.00 (s(br), 1H), 13.64 (s, 1H) ; MS m/z 262 (M^{+}+1).

Preparation of intermediates

Method (ii)

cyclopropanecarbohydrazide



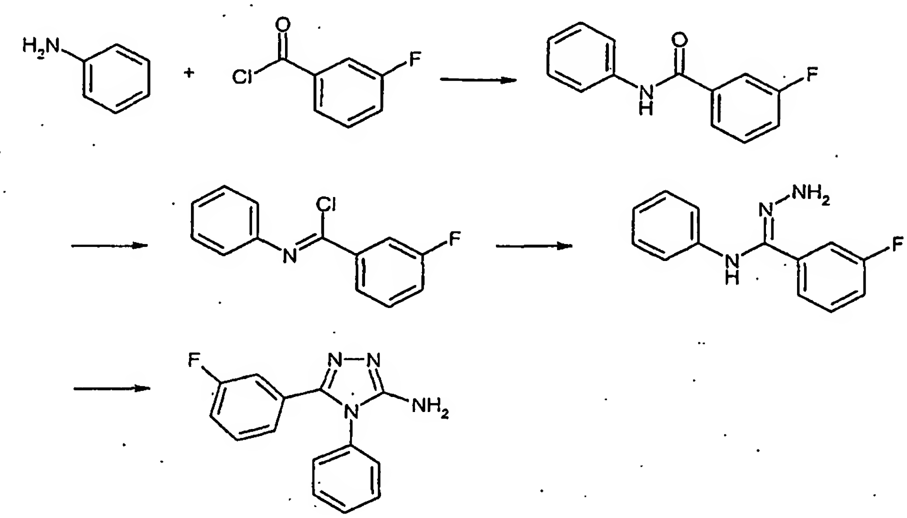
To a solution of tert-butyl hydrazinecarboxylate (6.38 g, 48.3 mmol) and triethylamine (7.26 g, 71.8 mmol) in dichloromethane (10 mL) was added cyclopropanecarbonyl chloride (5.00 g, 47.8 mmol) at 0 °C. The mixture was stirred for 16 hours at ambient temperature, and the resulting suspension was filtered and washed with dichloromethane. The filtrate was concentrated under reduced pressure to provide tert-butyl 2-(cyclopropylcarbonyl)hydrazinecarboxylate (13.0 g). ^{1}H NMR (DMSO-d_6) δ 0.67-0.72 (m, 4H), 1.39 (s, 1H), 1.52 -1.54 (m, 1H), 8.64 (s, 1H), 9.70 (s, 1H).

Next, to a stirred solution of tert-butyl 2-(cyclopropylcarbonyl)hydrazinecarboxylate (3.00 g, 15.0 mmol) in 1,4-dioxane (50 mL) was added 4N HCl in 1,4-dioxane (20 mL). The mixture was stirred at 80 °C for 1 hour, and after cooled to ambient temperature, it was concentrated under reduced pressure. To the obtained residue was added ethylacetate and triethylamine (8.04 g, 79.4 mmol), and the organic layer was washed with saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain cyclopropanecarbohydrazide (0.89 g).

Preparation of intermediates

Method (iv)

5-(3-fluorophenyl)-4-phenyl-4H-1,2,4-triazol-3-amine



To a solution of aniline (1.00 g, 10.7 mmol) and pyridine (0.849 g, 10.7 mmol) in dichloromethane (20 mL) was added 3-fluorobenzoyl chloride (1.70 g, 10.7 mmol) at 0 °C and stirred for 1 hour. After water was added, the mixture was extracted with dichloromethane. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain 3-fluoro-N-phenylbenzamide (2.45 g). ^{1}H NMR (DMSO-d_6) δ: 7.09-7.15(m, 1H), 7.33-7.40 (m, 2H), 7.41-7.49 (m, 1H), 7.55-7.64(m, 1H), 7.73-7.84 (m, 4H); m/z 216.15 (M^++1).

Next, a mixture of 3-fluoro-N-phenylbenzamide (1.00 g, 4.65 mmol) and thionyl chloride (3.4 mL) was heated at 80 °C for 16 hours. After cooled to ambient temperature, excess of thionyl chloride was removed under reduced pressure to obtain 3-fluoro-N-phenylbenzenecarboximidoyl chloride (1.00 g).

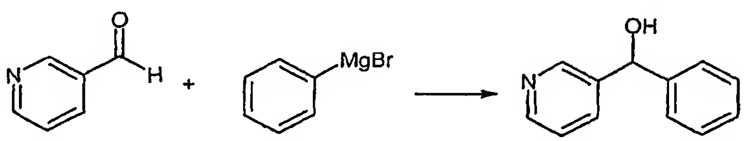
Next, to a solution of anhydrous hydrazine (2.72 g, 84.9 mmol) in benzene (15 mL) was added 3-fluoro-N-phenylbenzenecarboximidoyl chloride (0.800 g, 3.39 mmol) at 0 °C. After having stirred at room temperature for 16 hours, water was added and the mixture was extracted with diethylether. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide 3-fluoro-N-phenylbenzenecarbohydrazonamide (0.822 g).

Next, a mixture of 3-fluoro-N-phenylbenzenecarbohydrazonamide (200 mg, 0.65 mmól) and cyanogen bromide (69.3 mh, 0.65 mmol) in methanol (3 mL) was heated at 90 °C for 48 hours. After having cooled to ambient remperature, the mixture was concentrated under reduced pressure, and the obtained residue was purified by preparative TLC (eluent: dichloromethane / methanol = 95 / 5) to provide 5-(3-fluorophenyl)-4-phenyl-4H-1,2,4-triazol-3-amine (108 mg). ^{1}H NMR (DMSO-d_6) δ: 5.82 (s, 2H), 6.90 (t, J=7.3Hz, 1H), 6.98-7.27 (m, 3H), 7.28-7.42 (m, 3H), 7.52-7.54 (m, 2H); m/z 255.25 (M^++1).

Preparation of intermediates

Method (v)-1

Phenyl(pyridin-3-yl)methanol



To a solution of 3-pyridinecarboxaldehyde (1.00 g, 9.34 mmol) in tetrahydrofuran (50 mL) was added 1.09 M phenyl magnesium bromide in tetrahydrofuran solution (10.3 mL, 11.20 mmol). After the mixture was stirred at room temperature for 2 hours, water was added and extracted with ethylacetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography (eluent: dichloromethane / diethylether = 4 / 1) to provide phenyl(pyridin-3-yl)methanol (1.07 g). ^{1}H NMR (CDCl3-d): δ 3.85 (1H, s), 5.83 (1H, sz), 7.20-7.37 (6H, m), 7.69 (1H, ddd, J = 2.5, 2.5, 7.9 Hz), 8.38 (1H, dd, J = 2.5, 4.8 Hz), 8.51 (1H, d, J = 2.5 Hz); MS m/z 186 (M+1).

Method (v')-1

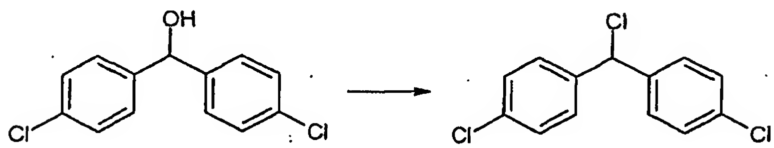
cyclobutyl(phenyl)methanol

To a solution of cyclobutyl(phenyl)methanone (1.00 g, 6.24 mmol) in methanol was added sodium borohydride (0.315 g, 7.49 mmol) at 0 °C. After the mixture was stirred for 1 hour at 0 °C, water was added and extracted with ethylacetate. The organic layer was dried over $MgSO_4$, filtered, and

concentrated under reduced pressure to obtain cyclobutyl(phenyl)methanol (1.03 g). ^{1}H NMR (CDCl3-*d*): δ 1.74-1.88 (4H, t, m), 1.91-2.15 (2H, m), 2.63 (1H, m), 4.57 (1H, d, J = 7.9 Hz), 7.23-7.35 (5H, m).

Method (v)-2

1,1'-(chloromethylene)bis(4-chlorobenzene)



To a solution of 4,4'-dichlorobenzhydrol (4.78 g, 18.9 mmol) in dichloromethane (400 mL) was added thionyl chloride (2.81 g, 23.6 mmol) and 1H-benzotriazole (2.81 g, 23.6 mmol) at room temperature. After the mixture was stirred for 10 minutes, it was filtered, and to the filtrate was added water and extracted with dichloromethane. The organic layer was washed with 3% aqueous sodium hydroxide solution, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide 1,1'-(chloromethylene)bis(4-chlorobenzene) (5.14 g). ^{1}H NMR (CDCl3-*d*): δ 6.05 (1H, s), 7.26-7.32 (8H, m).

In the similar manner as described in Example 1-1 and with the use of intermediates described above, compounds in Example 1-2 to 1-167 as shown in Table 1 were synthesized.

Table 1

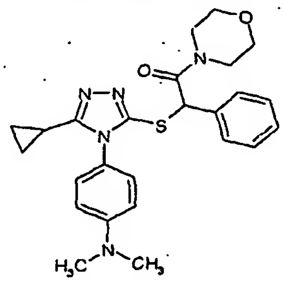
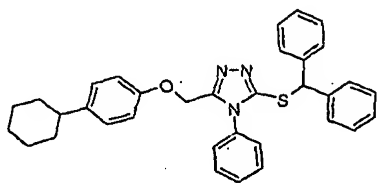
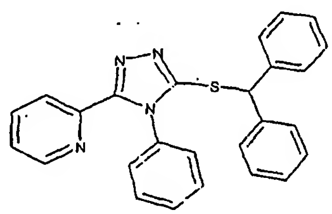
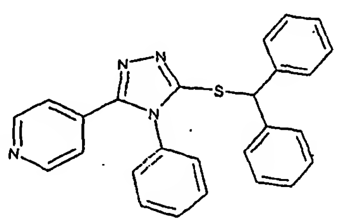
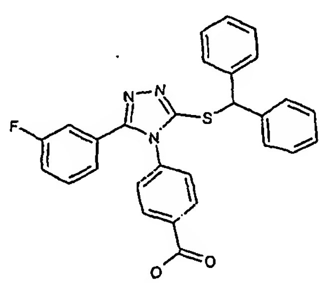
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-2		463,603	464	189,1	D
Example 1-3		531,721		Rt=6.07 (method2C)	D
Example 1-4		420,538		Rt=4.83 (method 2B)	B
Example 1-5		420,538		Rt=4.41 (method 2B)	B
Example 1-6		481,549		Rt=4.49 (method 2A)	B

Table 1

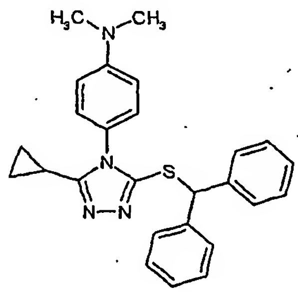
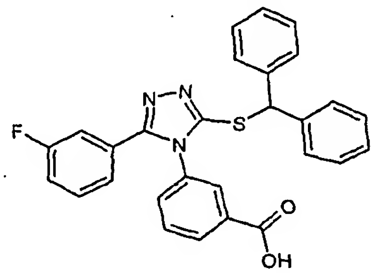
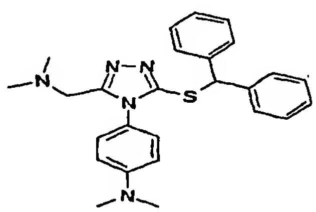
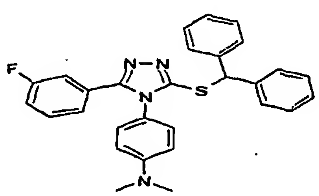
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-7		426,585	427	Rt = 2.82 (method A)	A
Example 1-8		481,549		Rt=4.52 (method 2A)	A
Example 1-9		443,6185	444	Rt = 2.75 (method A)	B
Example 1-10		480,6118	481	Rt = 2.92 (method A)	

Table 1

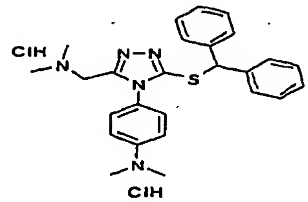
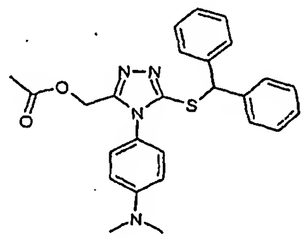
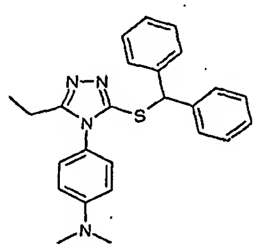
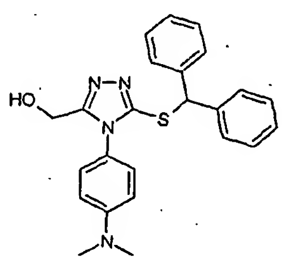
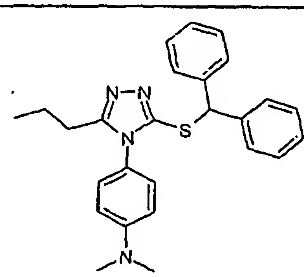
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-11		516,5405	444	207,8	B
Example 1-12		458,58	459,2	Rt = 2.85 (method B)	A
Example 1-13		414,57	415,2	82.1-86.5	A
Example 1-14		416,55	417,2	214.4-215.2	B
Example 1-15		428,6	429,3	81.2-84.6	A

Table 1

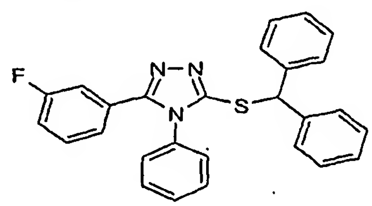
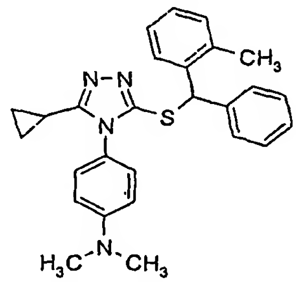
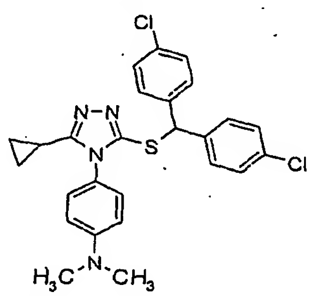
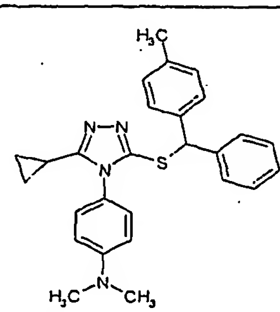
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-16		437,54	438,25	156-157	A
Example 1-17		440,612	441	48,7	A
Example 1-18		495,476	496	57,4	A
Example 1-19		440,612	441	60,8	A

Table 1

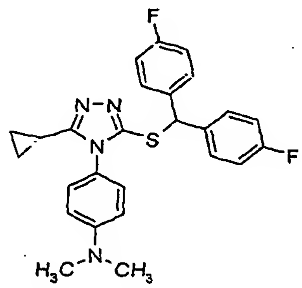
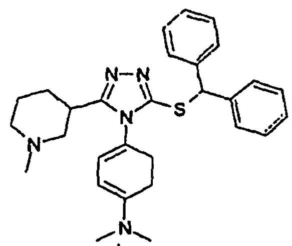
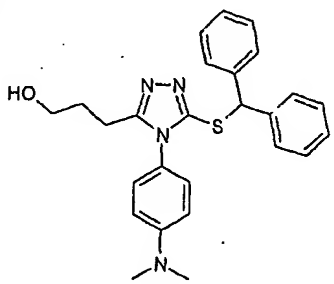
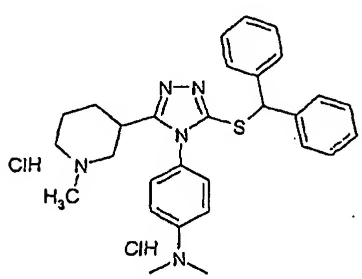
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-20		462,566	463	41,3	A
Example 1-21		485,6998	484	Rt = 2.58 (method A)	B
Example 1-22		446,6192	445	Rt = 2.54 (method A)	A
Example 1-23		558,6217	484	203,8	B

Table 1

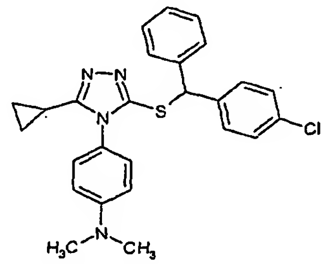
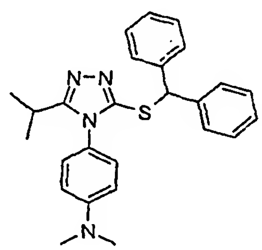
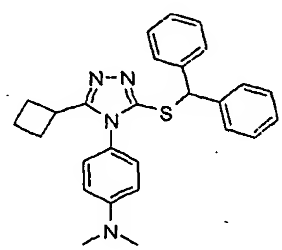
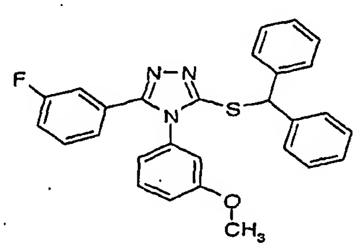
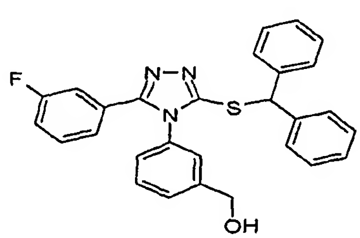
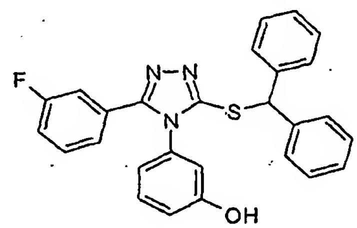
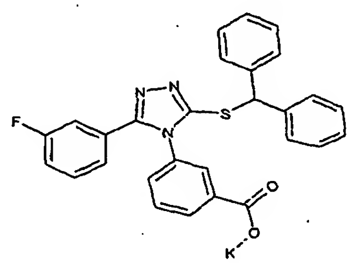
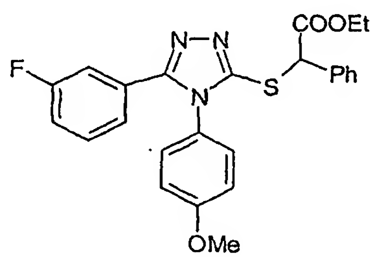
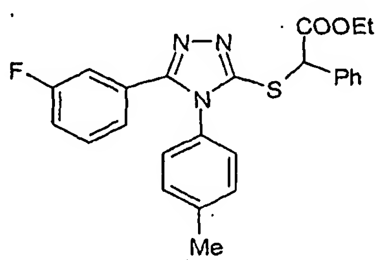
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-24		461,031	462	56,2	A
Example 1-25		428,6	429,3	135.8-138.6	A
Example 1-26		440,61	441,3	150.8-151.7	A
Example 1-27		467,57	468,2	169-170 (method B)	A
Example 1-28		467,57	468,2	Rt =3.21 (method B)	A

Table 1

Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-29		453,54	454,06	69-70	A
Example 1-30		519,65	32.2 (-38[K	>300	A
Example 1-31		463,53	464	Rt = 5.14 (method C)	D
Example 1-32		447,54	448	141-142	D

<u>Table 1</u>

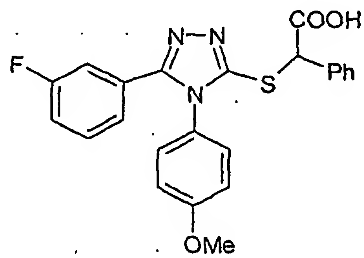
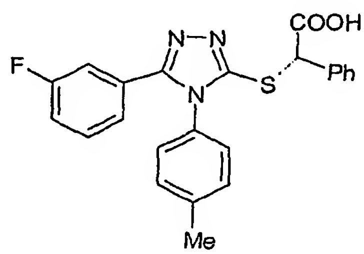
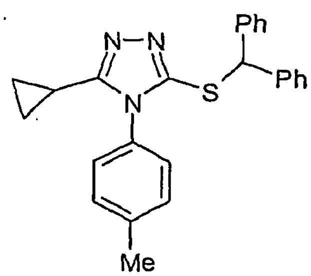
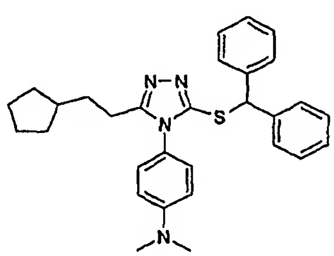
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-33		435,48	436	110-111	D
Example 1-34		419,48	420	88-89	D
Example 1-35		397,55	398	Rt = 5.08 (method C)	A
Example 1-36		482,693	483	146,8	A

Table 1

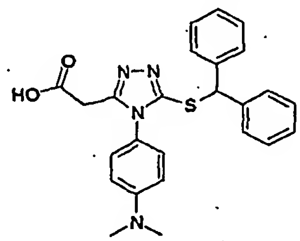
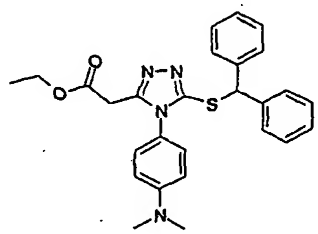
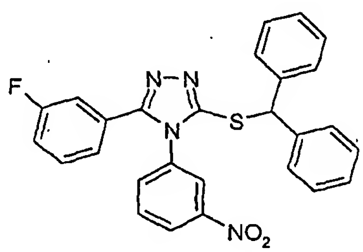
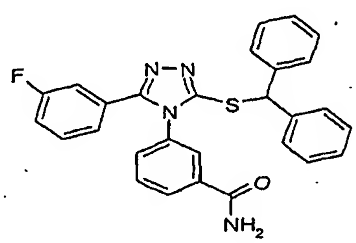
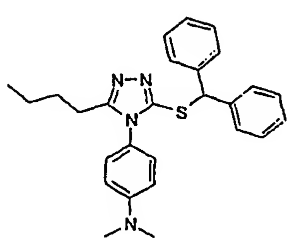
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-37		444,557	445	Rt = 2.2 (method A)	B
Example 1-38		472,61	473	Rt = 2.83 (method A)	B
Example 1-39		482,54	483,07	79-80	B
Example 1-40		480,57	481,12	81-82	A
Example 1-41		442,63	443,3	59.5-62.4	A

Table 1

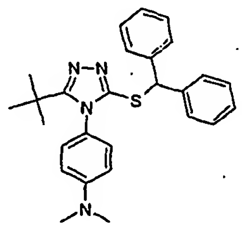
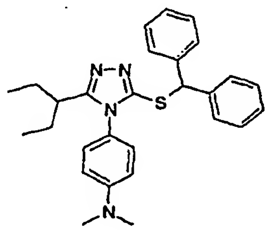
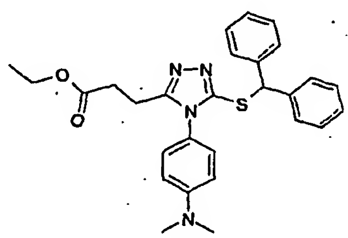
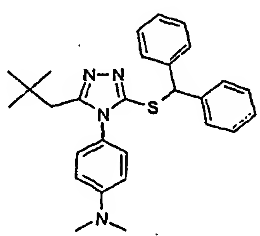
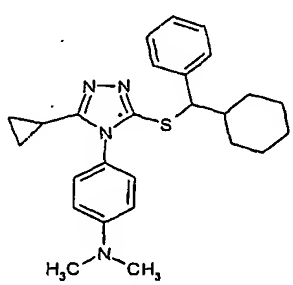
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-42		442,63	443,3	194-198.8	B
Example 1-43		456,66	457,3	108.2-109.1	D
Example 1-44		486,64	487,3	149.8-155.2	A
Example 1-45		456,66	457,3	126.4-127.2	B
Example 1-46		432,633	433	47,1	A

Table 1

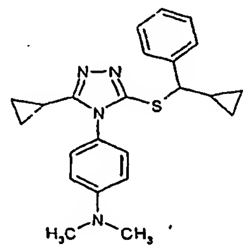
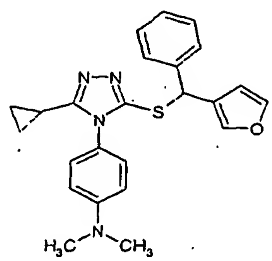
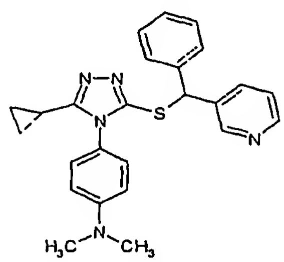
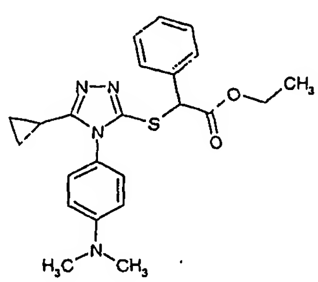
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-47		390,552	391	Rt = 3.39 (method B)	C
Example 1-48		416,547	417	Rt = 3.03 (method B)	A
Example 1-49		427,574	428	46,9	D
Example 1-50		422,55	423	50,9	D

Table 1

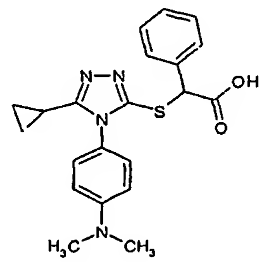
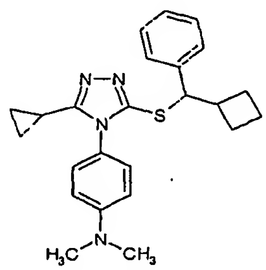
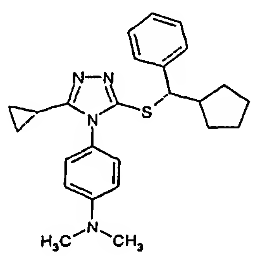
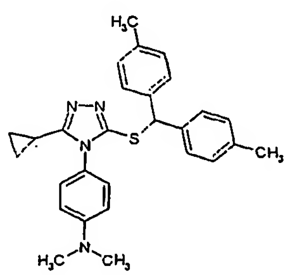
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-51		394,497	395	114,6	D
Example 1-52		404,579	405	Rt = 3.48 (method B)	A
Example 1-53		418,606	419	Rt = 3.57 (method B)	A
Example 1-54		454,639	455	46,6	A

Table 1

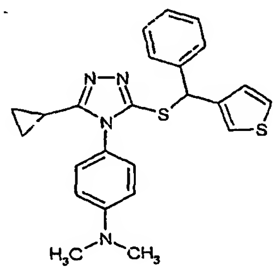
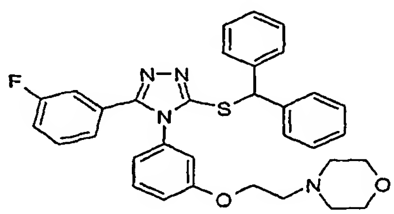
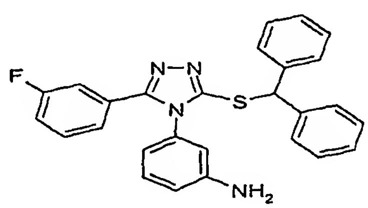
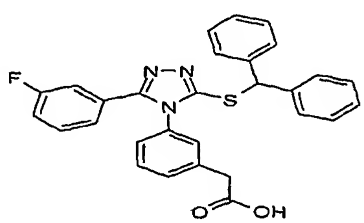
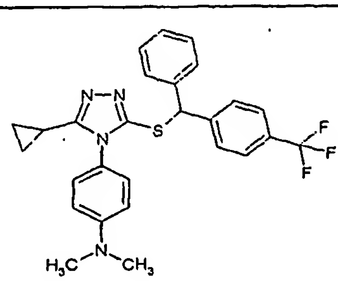
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-55		432,614	433	45	A
Example 1-56		566,7	567,17	Rt =2.81 (method A)	B
Example 1-57		452,56	453,08	Rt =2.74 (method A)	D
Example 1-58		495,58	496,08	Rt =2.28 (method A)	B
Example 1-59		494,583	495	54,2	A

Table 1

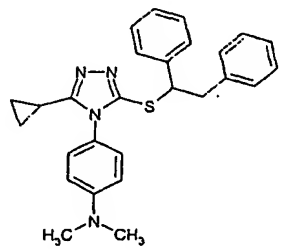
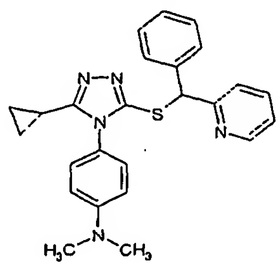
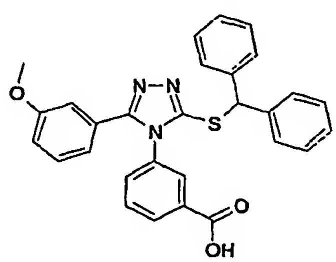
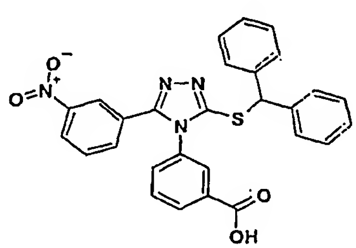
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-60		440,612	441	54,8	B
Example 1-61		427,574	428	79,9	A
Example 1-62		493,589	494	201,5	B
Example 1-63		508,56	509	211,1	B

Table 1

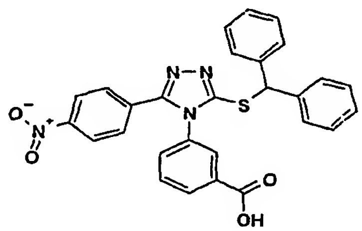
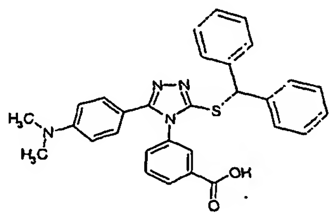
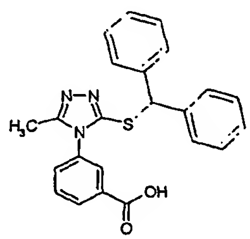
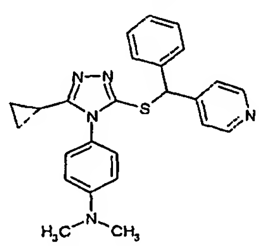
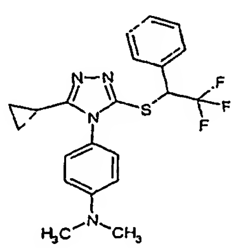
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-64		508,56	509	98,7	A
Example 1-65		506,6313	507,15	229.8-232.0	B
Example 1-66		401,4908	402,09	158.0-160.2	D
Example 1-67		427,574	428	45,8	A
Example 1-68		418,485	419	Rt = 2.75 (method B)	B

Table 1

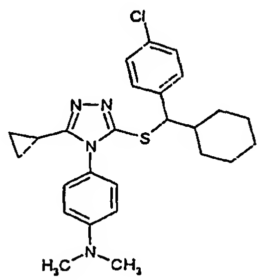
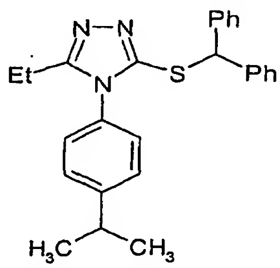
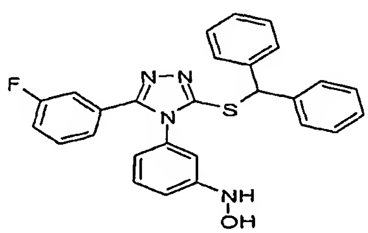
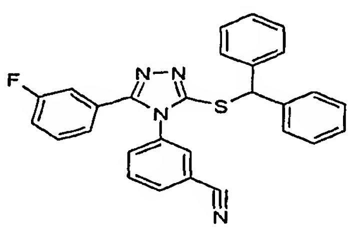
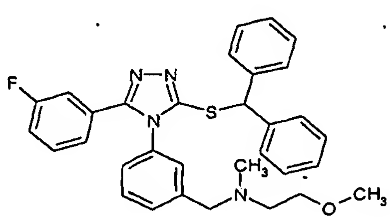
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-69		467,078	468	52,7	A
Example 1-70		413,59	414	Rt = 5.64 (method C)	A
Example 1-71		468,56	469,09	Rt = 2.64 (method A)	A
Example 1-72		462,55	463,09	62-63	A
Example 1-73		538,69	539,27	Rt = 3.19 (method B)	B

Table 1

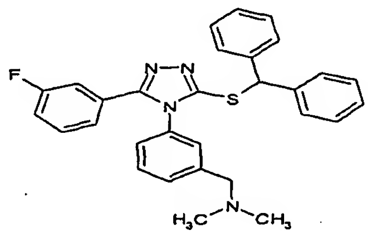
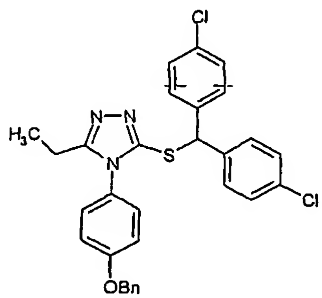
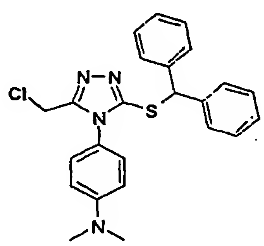
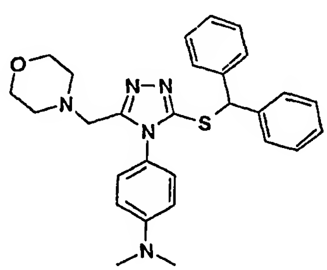
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-74		494,64	495,11	Rt = 2.85 (method A)	B
Example 1-75		546,519	547	126-127	B
Example 1-76		434,99	435,2	126.8-127.3	B
Example 1-77		485,65	486,3	54.0-57.9	B

Table 1

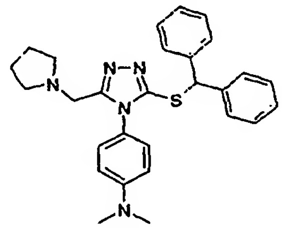
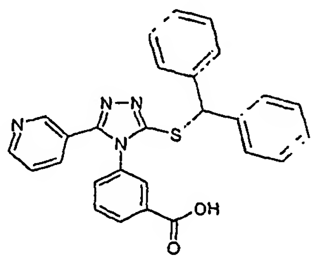
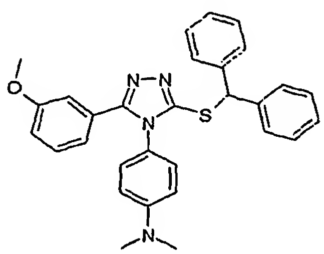
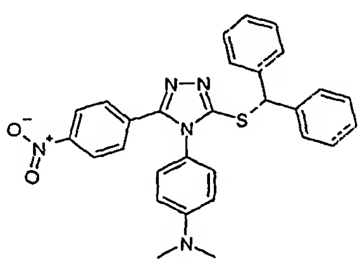
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-78		469,65	470,3	Rt = 3.17 (method B)	B
Example 1-79		464,547	465,07	196-198	D
Example 1-80		492,65	493	Rt = 2.96 (method A)	A
Example 1-81		507,62	508	179,1	A

Table 1

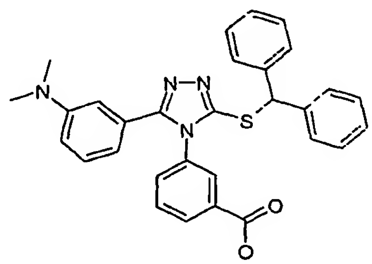
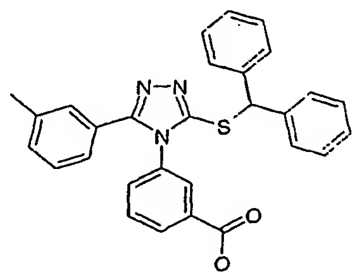
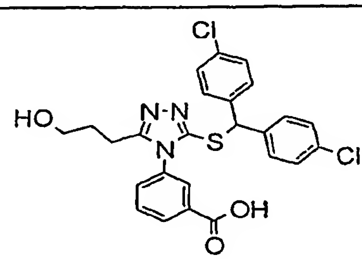
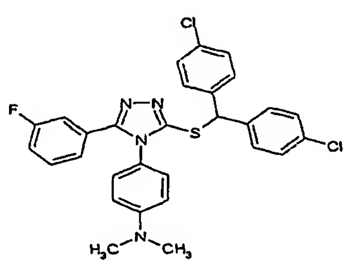
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-82		506,63	507	177,3	C
Example 1-83		477,59	478	Rt = 2.18 (method A)	A
Example 1-84		514,431	515	114,4	D
Example 1-85		549,499	550	69,5	A

Table 1

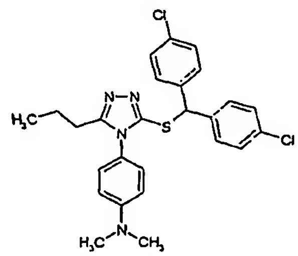
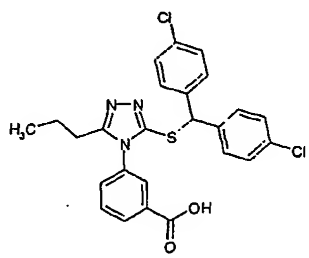
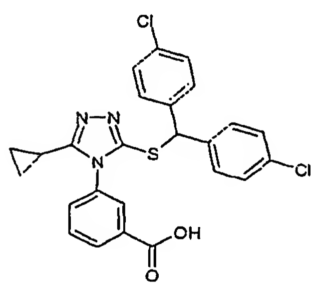
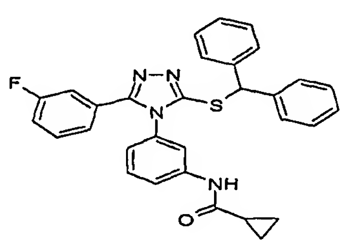
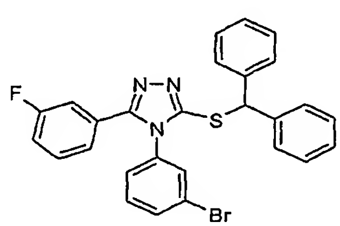
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-86		497,491	498	53,7	A
Example 1-87		498,432	499	201,6	A
Example 1-88		496,416	497	139,4	A
Example 1-89		520,63	521,2	95-96	A
Example 1-90		516,44	518,05	61-62	A

Table 1

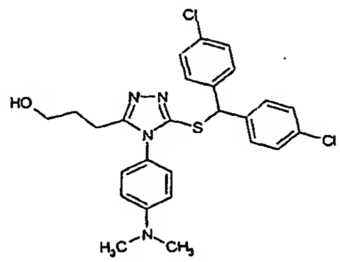
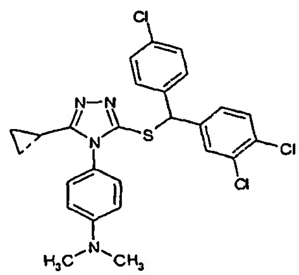
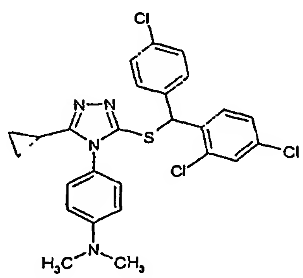
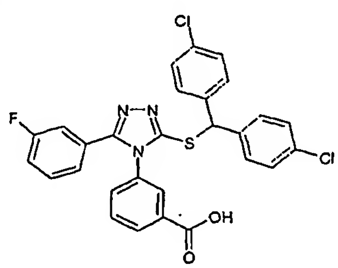
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-91		513,49	514	59,4	A
Example 1-92		529,92	530	58,1	A
Example 1-93		529,92	530	67,2	A
Example 1-94		550,439	551	235,4	A

Table 1

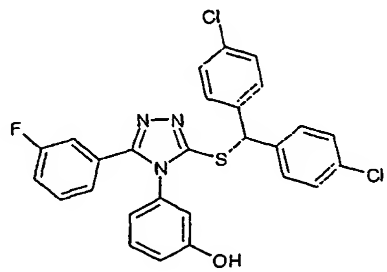
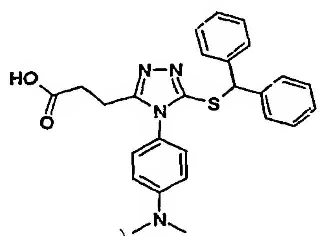
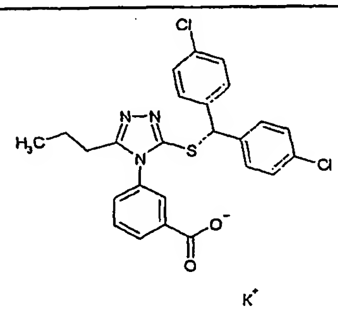
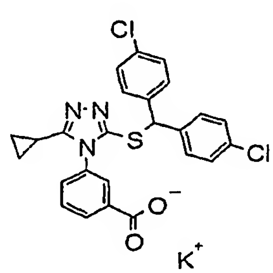
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-95		522,429	523	212	A
Example 1-96		458,58	459,2	98.7-103.7	B
Example 1-97		536,522	499	95,7	A
Example 1-98		534,506	467	127,2	A

Table 1

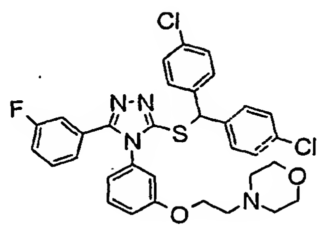
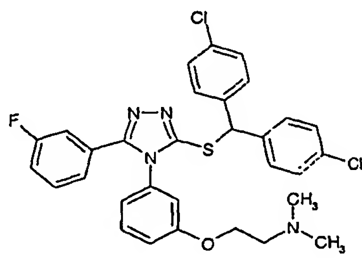
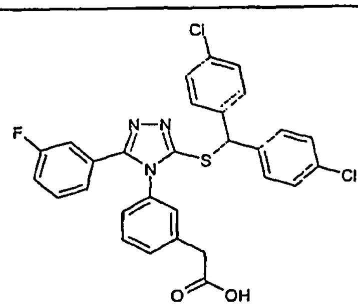
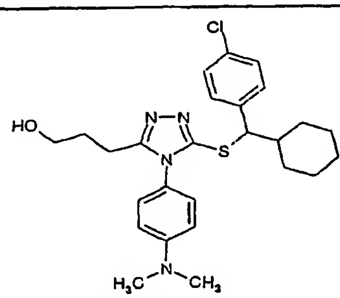
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-99		635,588	636	51,2	A
Example 1-100		593,551	594	48,5	A
Example 1-101		564,466	567	90,4	A
Example 1-102		485,093	486	53,4	A

Table 1

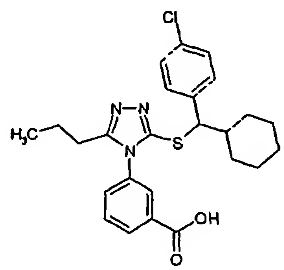
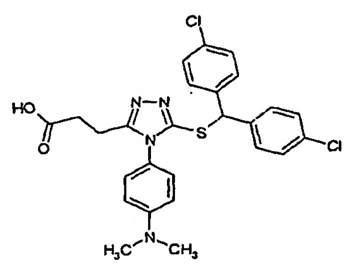
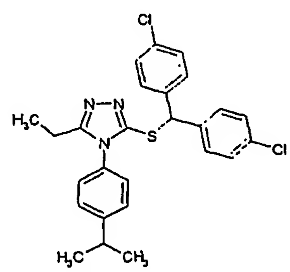
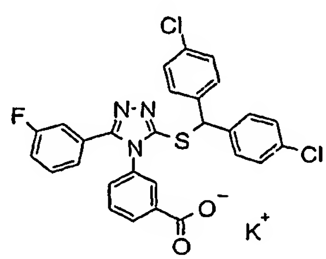
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-103		470,034	471	89,3	A
Example 1-104		527,474	528	109,5	D
Example 1-105		482,48	482	Rt = 6.13 (method C)	A
Example 1-106		588,529	551	164,5	A

Table 1

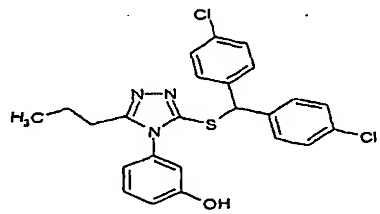
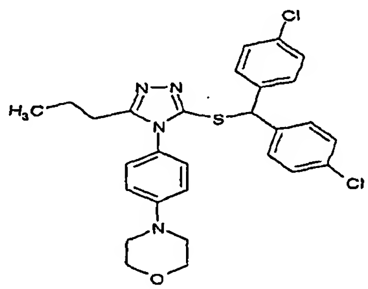
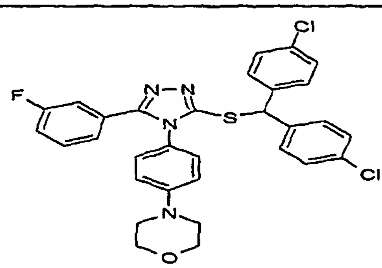
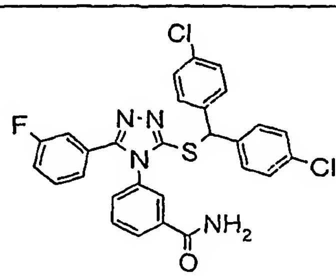
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-107		470,42	470,06	Rt = 2.73 (method A)	A
Example 1-108		539,53	539,11	60-61	B
Example 1-109		591,54	591,11	84-85	B
Example 1-110		549,455	550	204	A

Table 1

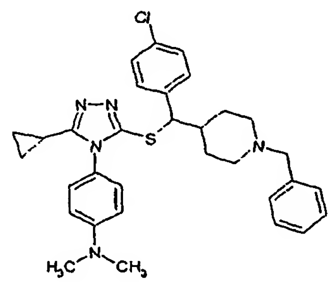
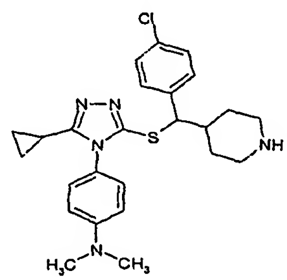
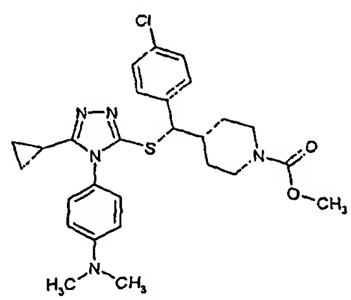
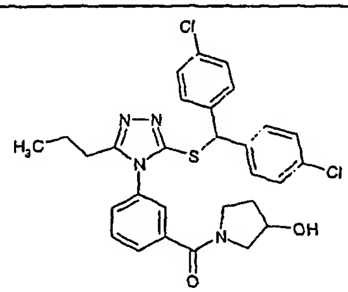
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-111		558,19	559	57,6	A
Example 1-112		468,066	469	146,8	D
Example 1-113		526,102	527	59,4	A
Example 1-114		567,538	568	60,5	A

Table 1

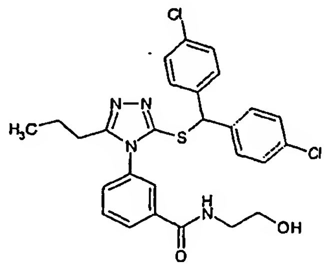
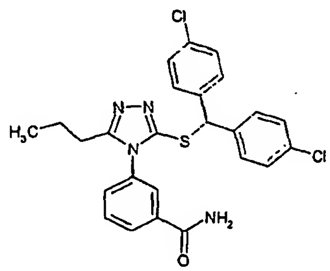
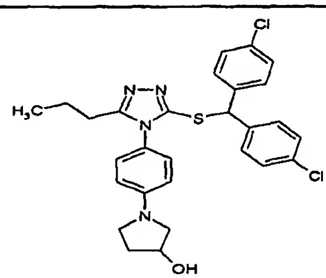
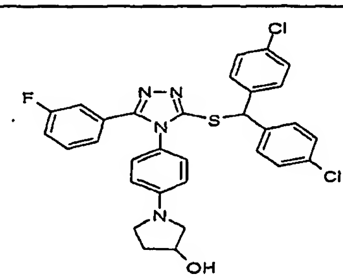
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-115		541,5	542	70,3	A
Example 1-116		497,448	498	90,3	A
Example 1-117		539,53	539,09	84-85	A
Example 1-118		591,54	591,06	108-109	A

Table 1

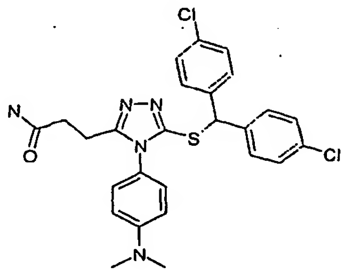
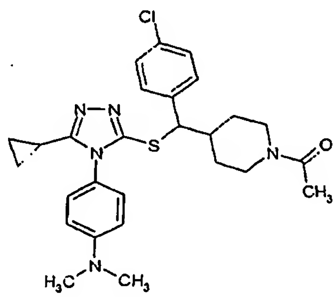
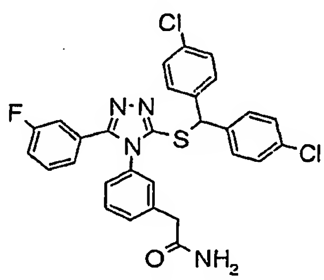
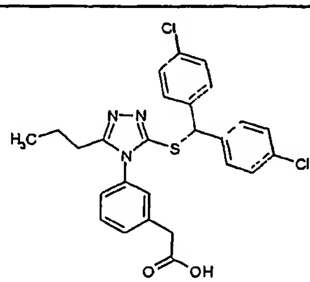
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-119		526,49	526(M), 528(M+2)	204,4	A
Example 1-120		510,103	511	74,6	B
Example 1-121		563,482	564	75,5	A
Example 1-122		512,459	513	75,5	A

Table 1

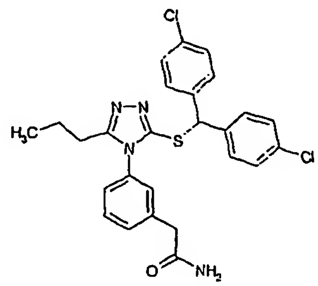
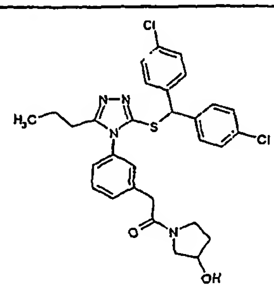
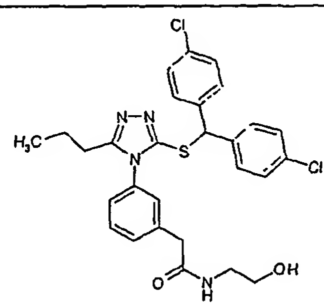
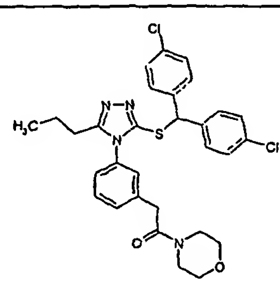
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-123		511,475	512	61,4	A
Example 1-124		581,565	582	82,3	A
Example 1-125		555,527	556	53	A
Example 1-126		581,565	582	56,4	A

Table 1

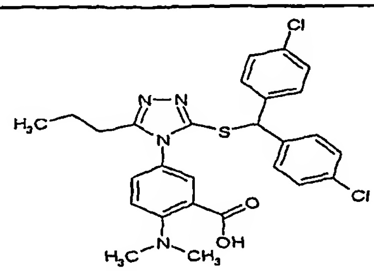
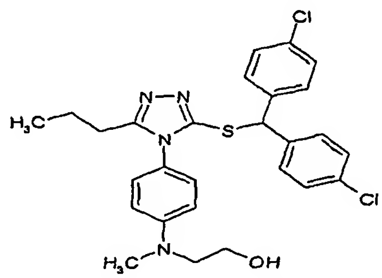
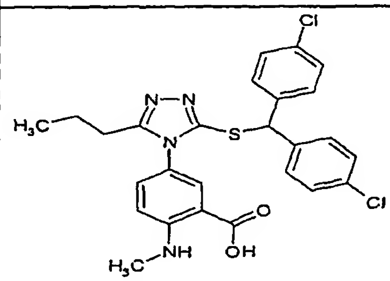
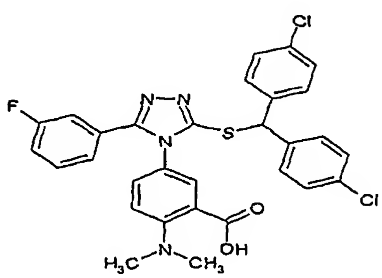
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-127		541,5	541,1	Rt =2.36 (method A)	A
Example 1-128		527,52	527,11	Rt =2.77 (method A)	A
Example 1-129		527,47	527,04	Rt =2.42 (method A)	A
Example 1-130		593,51	593,08	Rt =2.49 (method A)	A

Table 1

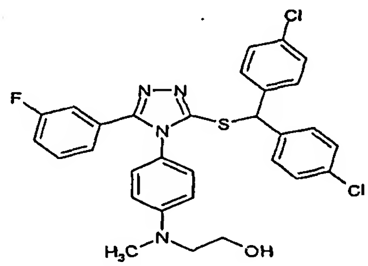
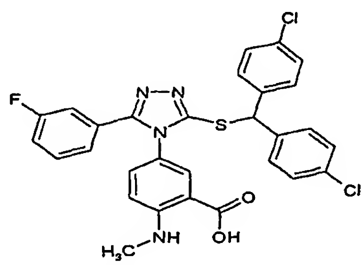
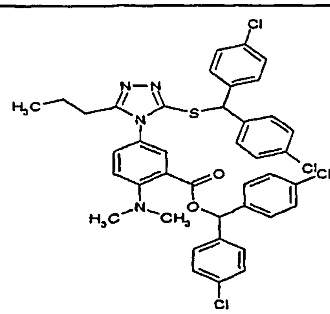
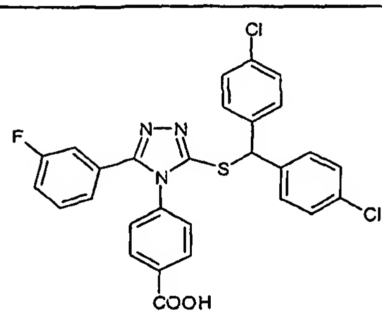
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-131		579,52	579,09	Rt =2.82 (method A)	A
Example 1-132		579,48	579,09	Rt =2.47 (method A)	A
Example 1-133		776,613	777,01	Rt =3.46 (method A)	
Example 1-134		550,409	551	247-249	A

Table 1

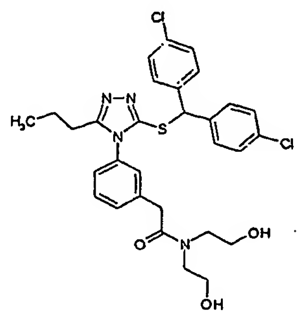
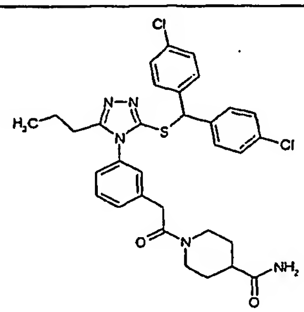
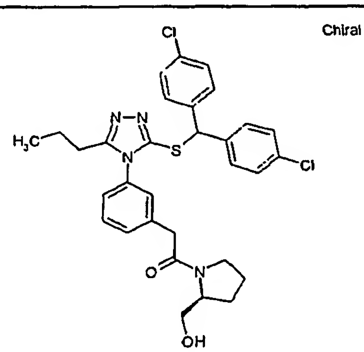
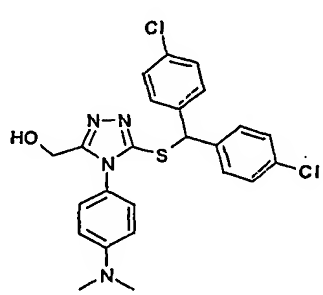
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-135		599,58	600	44,8	B
Example 1-136		622,618	623	100,4	B
Example 1-137		595,592	596	58,9	A
Example 1-138		485,44	485,1	205.2-210	

Table 1

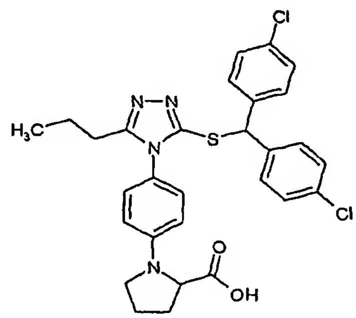
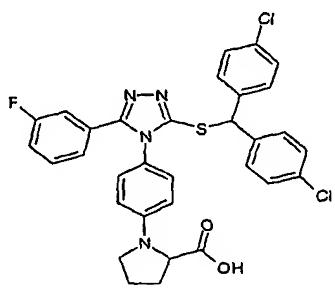
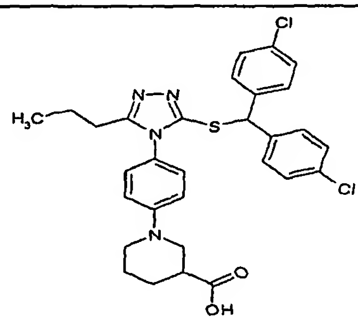
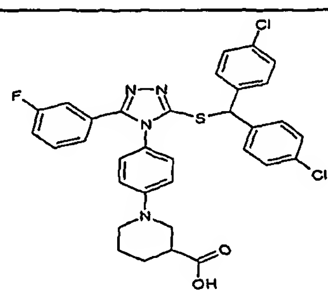
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-139		567,54	568	122	A
Example 1-140		619,54	620	87	A
Example 1-141		581,57	582	86	A
Example 1-142		633,57			A

Table 1

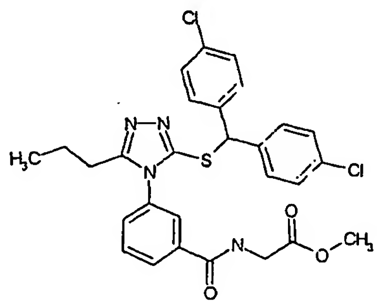
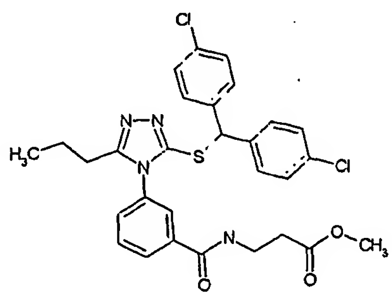
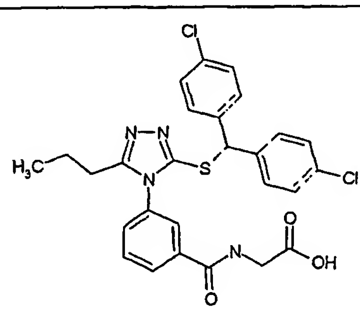
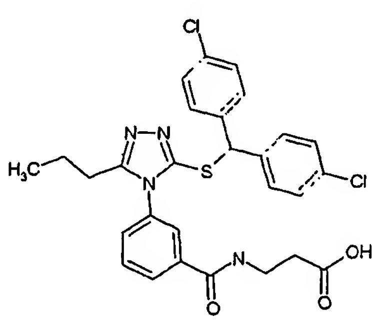
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-143		569,5144	570	83.6-86.1	A
Example 1-144		583,5415	584	61.1-62.9	A
Example 1-145		555,4873	556	110-113	B
Example 1-146		569,5144	570	95-98	A

Table 1

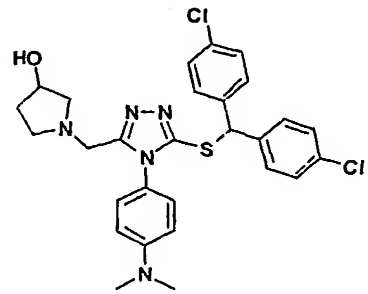
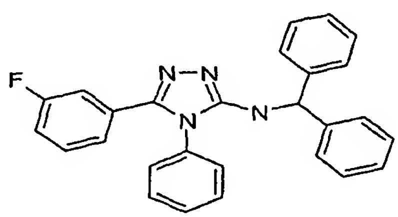
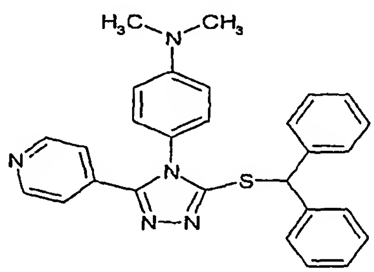
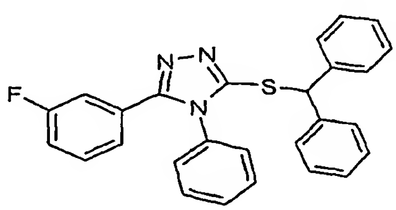
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-147		554,54	555	66.7-72-3	A
Example 1-148		420,49	421	177.5-178.4	
Example 1-149				Rt=4.44 (method 2C)	
Example 1-150				Rt=5.01 (method 2A)	

Table 1

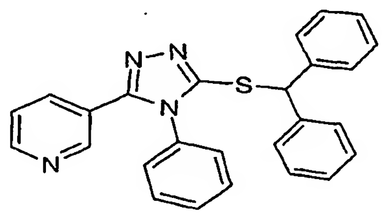
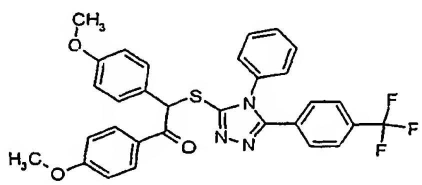
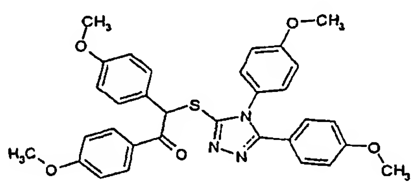
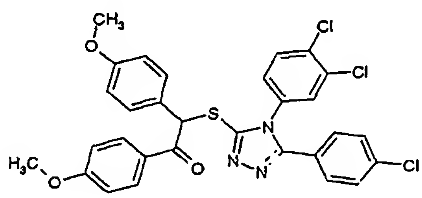
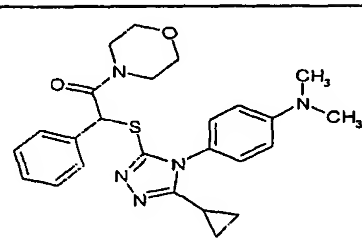
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-151				Rt=4.52 (method 2B)	
Example 1-152				Rt=4.48 (method 2D)	A
Example 1-153				Rt=4.25 (method 2D)	B
Example 1-154				Rt=4.64 (method 2D)	B
Example 1-155				Rt=3.61 (method 2D)	D

Table 1

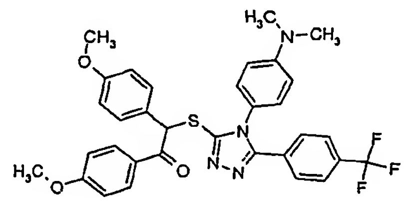
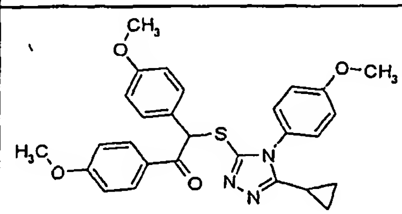
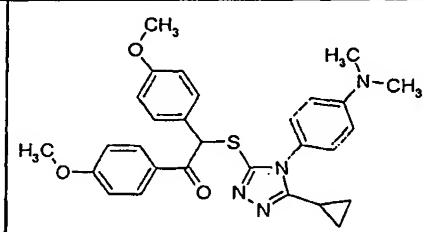
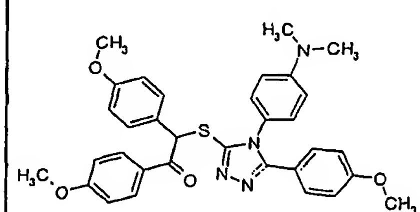
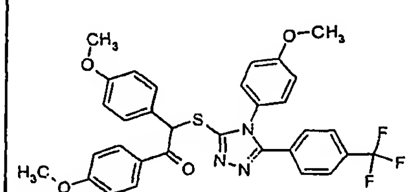
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-156				Rt=4.56 (method 2D)	A
Example 1-157				Rt=4.08 (method 2D)	A
Example 1-158				Rt=4.19 (method 2D)	A
Example 1-159				Rt=4.35 (method 2D)	A
Example 1-160				Rt=4.47 (method 2D)	A

Table 1

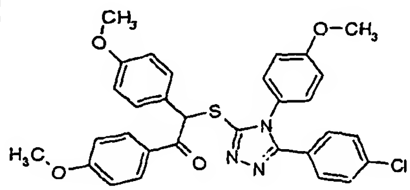
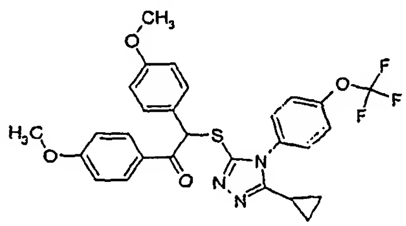
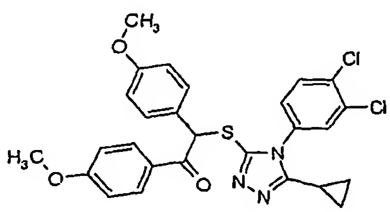
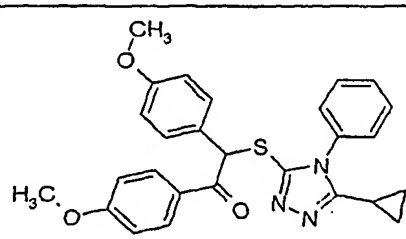
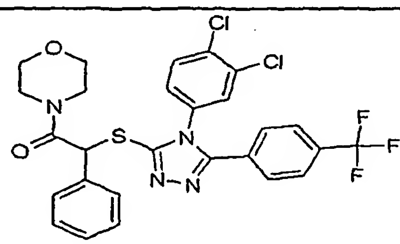
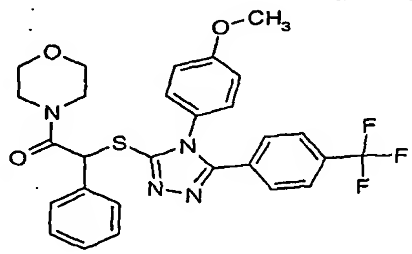
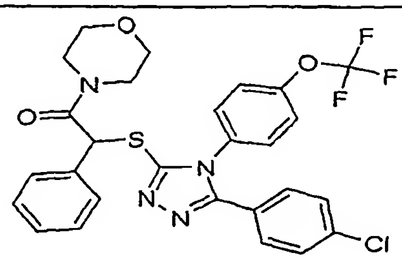
Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-161				Rt=4.43 (method 2D)	A
Example 1-162				Rt=4.35 (method 2D)	A
Example 1-163				Rt=4.37 (method 2D)	B
Example 1-164				Rt=4.06 (method 2D)	B
Example 1-165				Rt=4.40 (method 2D)	B

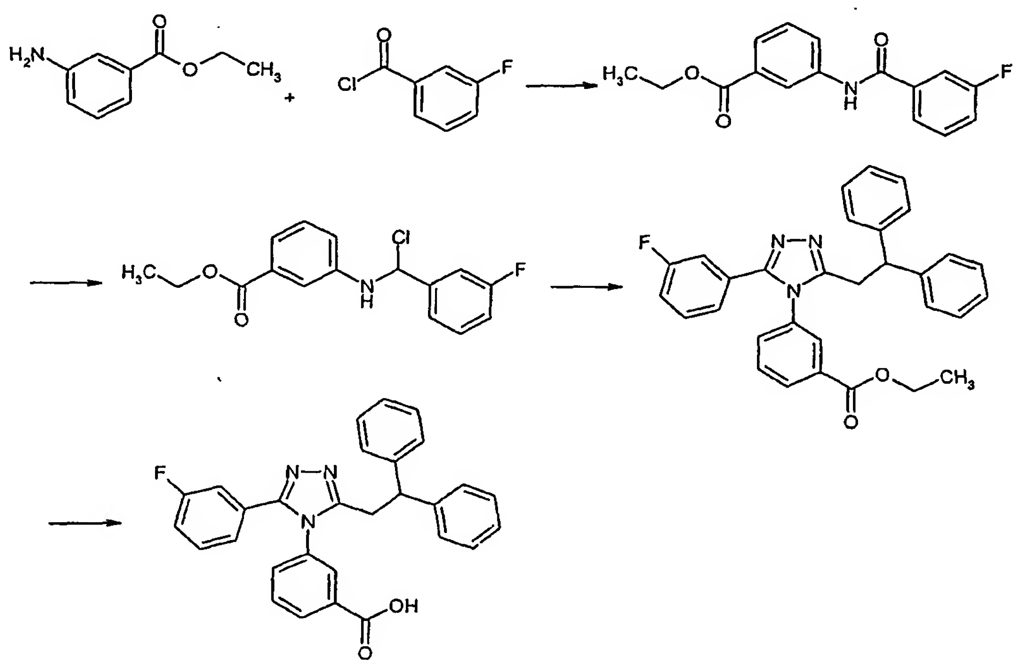
Table 1

Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 1-166				Rt=4.07 (method 2D)	D
Example 1-167				Rt=4.27 (method 2D)	D

[Example 2-1]

Method B

3-[3-(2,2-diphenylethyl)-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]benzoic acid



To solution of ethyl m-aminobenzoate (5.36 g, 32.4 mmol) in tetrahydrofuran (100 mL) was added 1-hydroxybenzotriazole (7.67 g, 56.8 mmol), triethylamine (3.61 g, 35.7 mmol), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (10.9 g, 56.8 mmol), and m-fluorobenzoic acid (5.00 g, 35.7 mmol) at room temperature and stirred for 4 hours. After water was added, the mixture was extracted with ethylacetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain ethyl 3-[(3-fluorobenzoyl)amino]benzoate.

Next, a mixture of ethyl 3-[(3-fluorobenzoyl)amino]benzoate (1.11 g, 3.86 mmol) and thionyl chloride was heated at 80 °C for 16 hours. After cooled to room temperature, the excess of thionyl chloride was removed underreduced pressure and obtained ethyl 3-{[(1E,Z)-chloro(3-fluorophenyl)methylene]amino}benzoate

(1.11 g).

Next, to a solution of ethyl 3-{[(1E,Z)-chloro(3-fluorophenyl)methylene]amino}benzoate (320 mg, 1.04 mmol) in acetonitrile (5 mL) was added 3,3-diphenylpropanohydrazide (300 mg, 1.25 mmol) and the mixture was heated to 90 °C for 16 hours. After having cooled to ambient temperature, the

mixture was concentrated under reduced pressure. The obtained residue was purified twice by preparative TLC (eluent: dichloromethane / methanol = 95 / 5 and then with ethylacetate / hexane = 1 / 1) to provide ethyl 3-[3-(2,2-diphenylethyl)-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]benzoate (78.0 mg). ^{1}H NMR (DMSO-d_6) δ: 1.31 (t, J=7.3Hz, 3H), 3.36 (d, J=7.6Hz, 2H), 4.32 (q, J=7.3Hz, 2H), 4.45 (t, J=8.2Hz, 1H), 7.04 (d, J=7.9Hz, 1H), 7.08-7.24 (m, 12H), 7.33-7.38 (m, 1H), 7.57-7.59 (m, 1H), 7.68 (t, J=1.9Hz, 1H), 7.72 (t, J=7.9Hz, 1H), 8.15 (d, J=7.9Hz, 1H); m/z 492.2 (M^++1).

To a solution of ethyl 3-[3-(2,2-diphenylethyl)-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]benzoate (72.0 mg, 0.15 mmol) in ethanol (2 mL) was added 1N aqueous sodium hydroxide solution at room temperature and stirred for 16 hours. The mixture was concentrated under reduced pressure, neutralized with 1N HCl aqueous solution, and extracted with ethylacetate. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The obtained residue was purified by preparative TLC (eluent: dichloromethane / methanol = 95 / 5) to provide 3-[3-(2,2-diphenylethyl)-5-(3-fluorophenyl)-4H-1,2,4-triazol-4-yl]benzoic acid (37.0 mg).

^{1}H NMR (DMSO-d_6) δ: 3.36 (d, J=7.8Hz, 2H), 4.44 (t, J=7.9Hz, 1H), 7.03-7.22 (m, 13H), 7.35 (q, J=7.9Hz, 1H), 7.52 (d, J=7.9Hz, 1H), 7.67-7.72 (m, 2H), 8.11 (d, J=7.9Hz, 1H).

mp 233-234 °C;

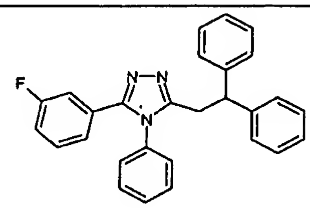
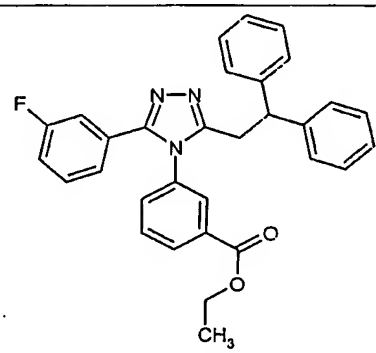
Molecular weight : 463.51

MS (M+H): 464

Activity Class : D

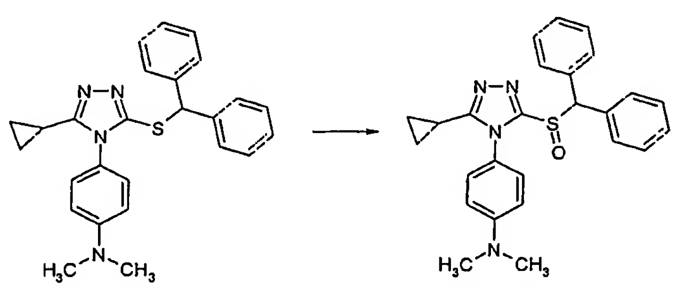
In the similar manner as described in Example 2-1, compounds in Example 2-2 to 2-3 as shown in Table 2 were synthesized.

Table 2

Example No.	Structure	MW	MS (M+1)	Melting Point or HPLC retention time (Rf)	Activity class
Example 2-2.		419,5	420,3	128-129	D
Example 2-3.		491,56	492,2	Rt =2.92 (method B)	D

Example 3-1

(4-{3-cyclopropyl-5-[(diphenylmethyl)sulfinyl]-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine



To a stirred suspension of (4-{3-cyclopropyl-5-[(diphenylmethyl)thio]-4H-1,2,4-triazol-4-yl}phenyl)dimethylamine (370 mg, 0.87 mmol) in dichloromethane was added m-chloroperoxybenzoic acid (374 mg, 2.17 mmol) at room temperature. After the mixture was stirred for 16 hours, it was filtered, and the filtrate was washed with sodium bicarbonate solution, water, and then with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to

obtain (4-{3-cyclopropyl-5-[(diphenylmethyl)sulfinyl]-4H-1,2,4-triazol-4-yl}phenyl)dimethyl-amine (326 mg).

^{1}H NMR (DMSO-d_6) δ 0.83-0.90 (m, 4H), 1.49-1.54 (m, 1H), 3.54(s, 6H), 5.87 (s, 1H), 7.22-7.31(m, 10H), 7.44 (d, J = 8.6 Hz, 2H), 8.30 (d, J = 8.6 Hz, 2H).

Molecular weight : 442.58

MS (M+H): 443

Activity Class : A

In the similar manner as described above and with the use of intermediates described above, compounds in Example 4-1 to 4-73 as shown in Table 3 were synthesized.

Table 3

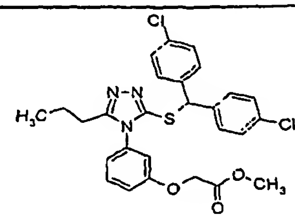
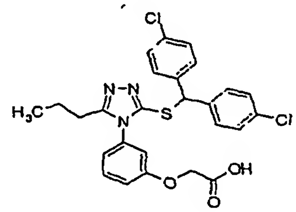
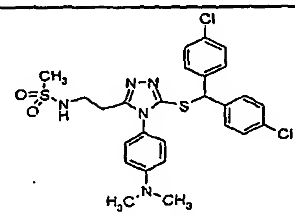
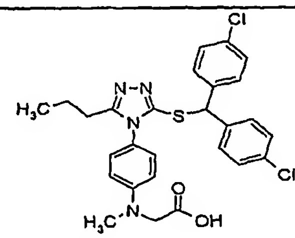
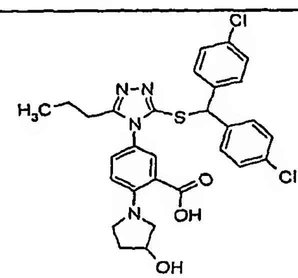
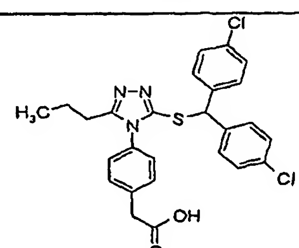
Example No.	Structure	Molecular Weight	Activity Class
4-1		542,48	A
4-2		528,46	A
4-3		576,57	A
4-4		541,50	A
4-5		583,54	A
4-6		512,46	A

Table 3

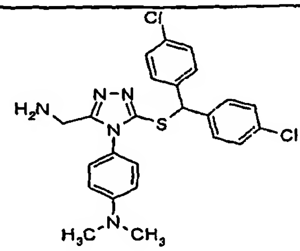
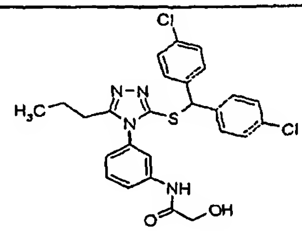
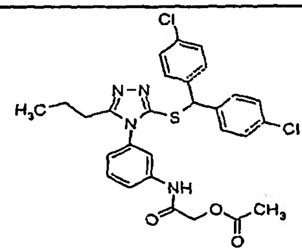
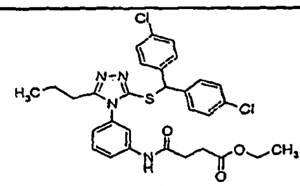
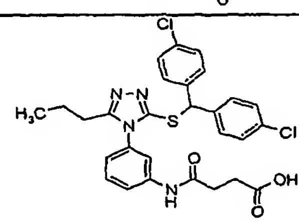
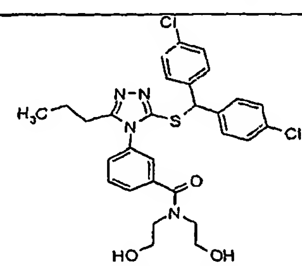
Example No.	Structure	Molecular Weight	Activity Class
4-7		484,45	A
4-8		527,47	A
4-9		569,51	A
4-10		597,56	A
4-11		569,51	A
4-12		585,55	A

Table 3

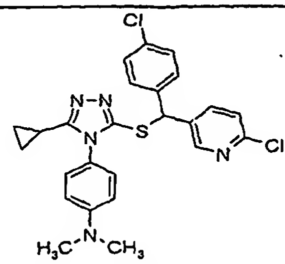
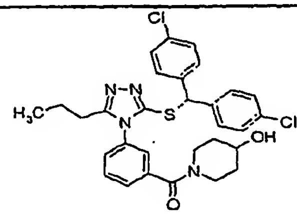
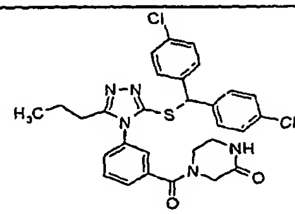
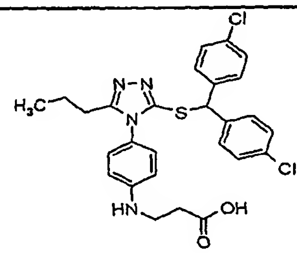
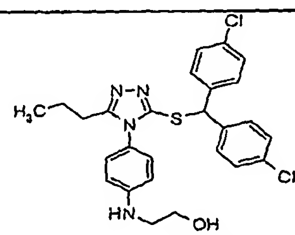
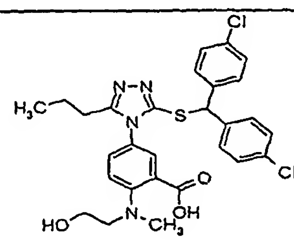
Example No.	Structure	Molecular Weight	Activity Class
4-13		496,46	A
4-14		581,57	A
4-15		580,54	A
4-16		541,50	A
4-17		513,49	A
4-18		571,53	A

Table 3

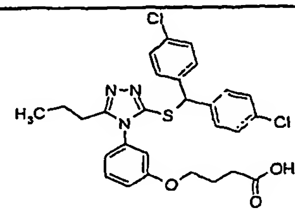
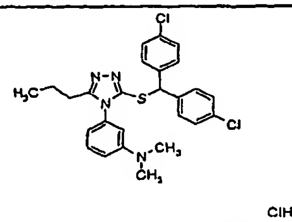
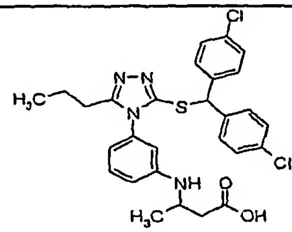
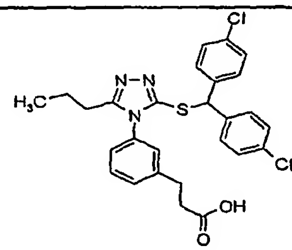
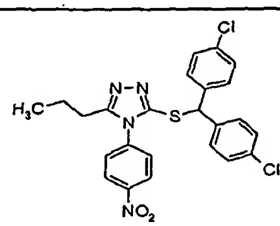
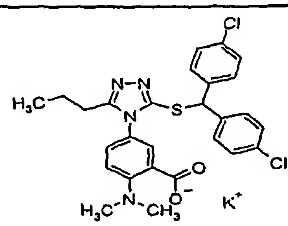
Example No.	Structure	Molecular Weight	Activity Class
4-19		556,51	A
4-20		533,95	A
4-21		555,53	A
4-22		526,49	A
4-23		499,42	A
4-24		579,59	A

Table 3

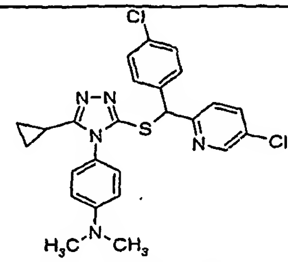
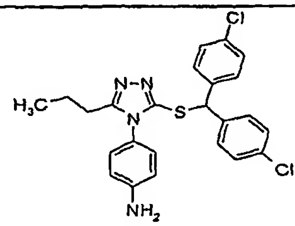
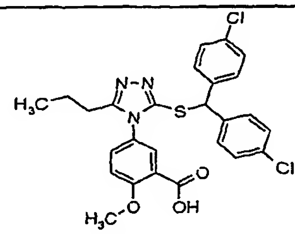
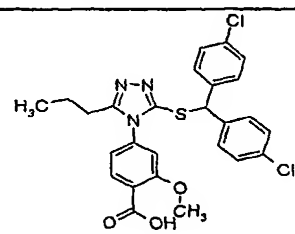
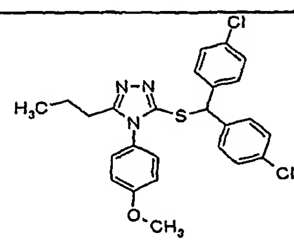
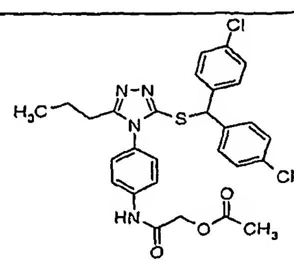
Example No.	Structure	Molecular Weight	Activity Class
4-25		496,46	A
4-26		469,44	A
4-27		528,46	A
4-28		528,46	A
4-29		484,45	A
4-30		569,51	A

Table 3

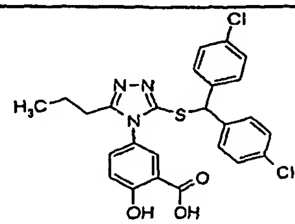
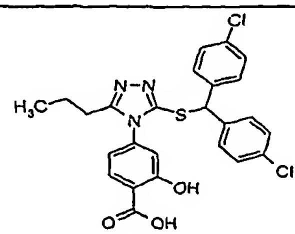
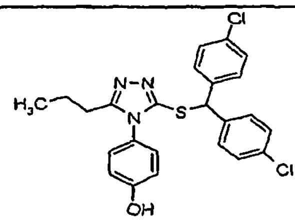
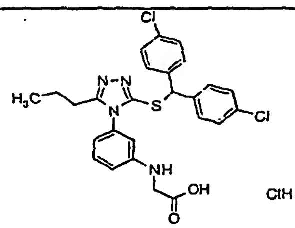
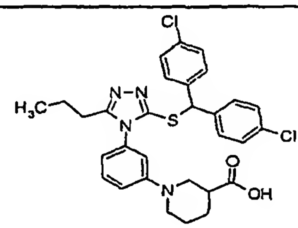
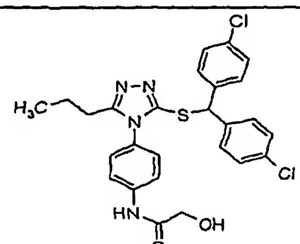
Example No.	Structure	Molecular Weight	Activity Class
4-31		514,43	A
4-32		514,43	A
4-33		470,42	A
4-34		563,94	A
4-35		581,57	A
4-36		527,47	A

Table 3

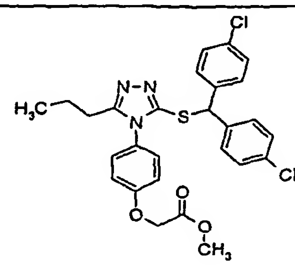
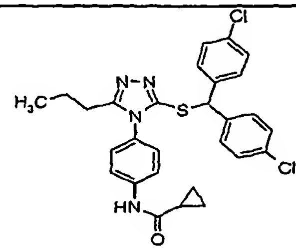
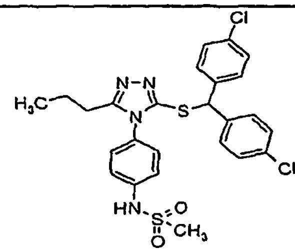
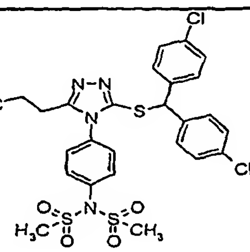
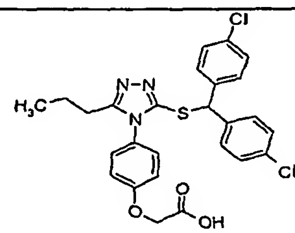
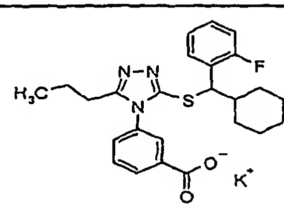
Example No.	Structure	Molecular Weight	Activity Class
4-37		542,48	A
4-38		537,51	A
4-39		547,53	A
4-40		625,62	A
4-41		528,46	A
4-42		491,67	B

Table 3

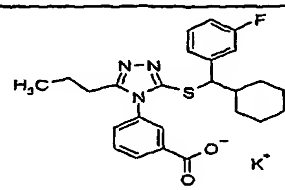
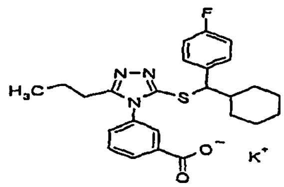
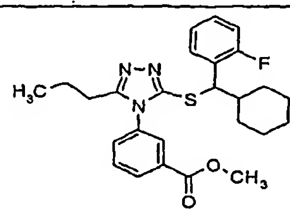
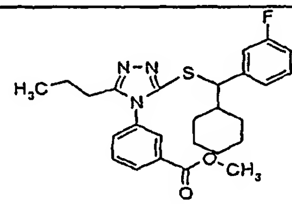
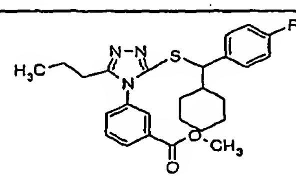
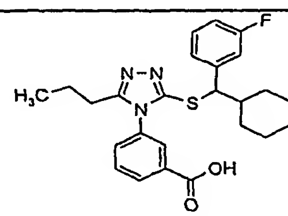
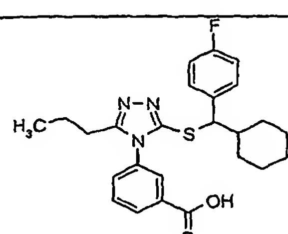
Example No.	Structure	Molecular Weight	Activity Class
4-43		491,67	A
4-44		491,67	A
4-45		467,61	B
4-46		467,61	A
4-47		467,61	A
4-48		453,58	A
4-49		453,58	A

Table 3

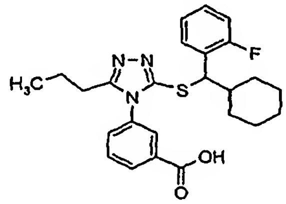
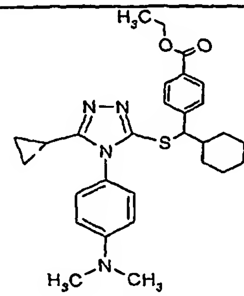
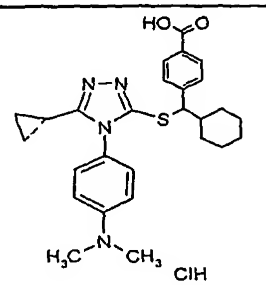
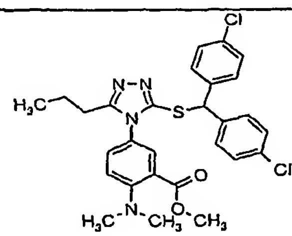
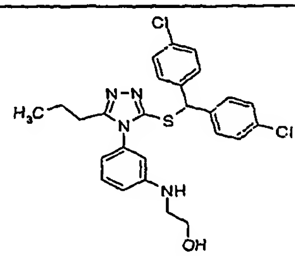
Example No.	Structure	Molecular Weight	Activity Class
4-50		453,58	B
4-51		504,70	A
4-52		513,10	B
4-53		555,53	A
4-54		513,49	A

Table 3

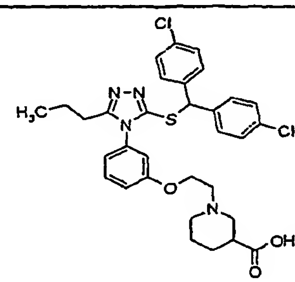
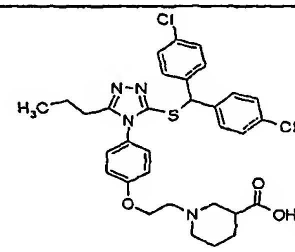
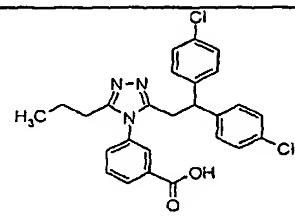
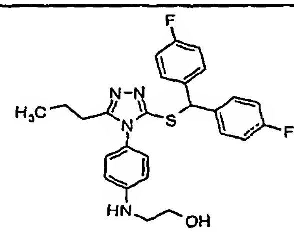
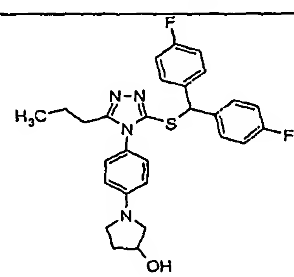
Example No.	Structure	Molecular Weight	Activity Class
4-55		625,62	A
4-56		625,62	A
4-57		480,40	B
4-58		480,58	A
4-59		506,62	A

Table 3

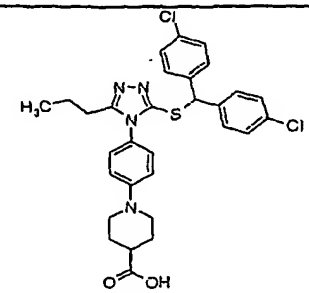
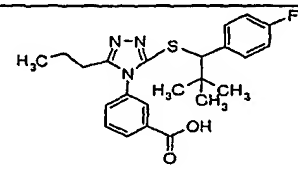
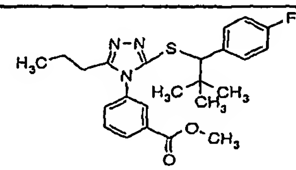
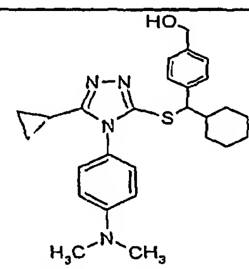
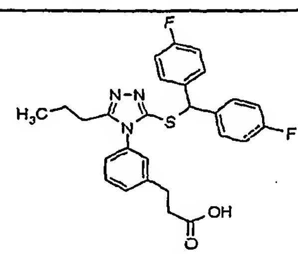
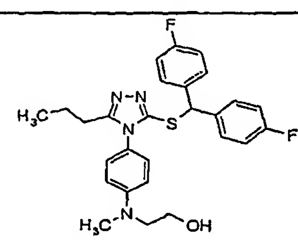
Example No.	Structure	Molecular Weight	Activity Class
4-60		581,57	A
4-61		427,54	A
4-62		441,57	A
4-63		462,66	A
4-64		493,58	A
4-65		494,61	A

Table 3

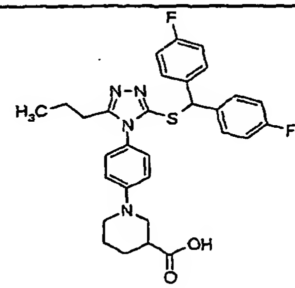
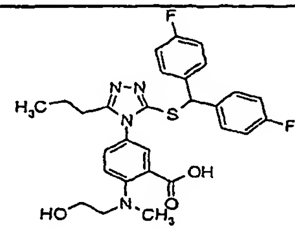
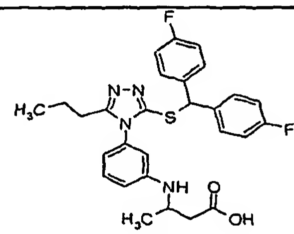
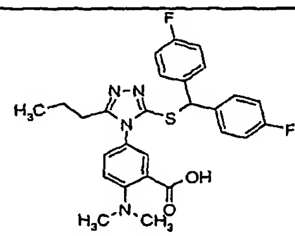
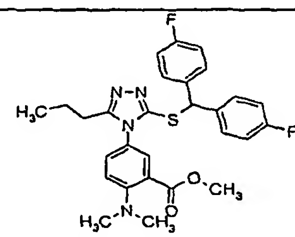
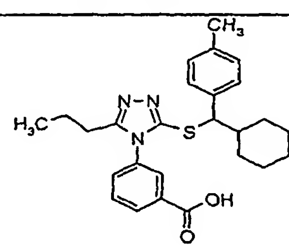
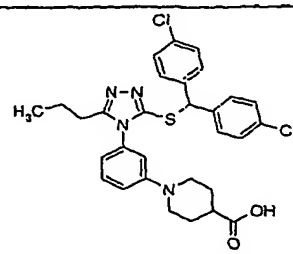
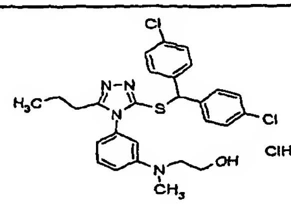
Example No.	Structure	Molecular Weight	Activity Class
4-66		548,66	A
4-67		538,62	A
4-68		522,62	A
4-69		508,59	A
4-70		522,62	A
4-71		449,62	A

Table 3

Example No.	Structure	Molecular Weight	Activity Class
4-72		581,57	A
4-73		563,98	A